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Docket No. 1010-102US4

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Kati A. Chevaux, et al.

Filed: 03/01/2004

Group Art Unit: 1655

Serial No: 10/790,289

Examiner: R. O. Winston

For: Products Containing Polyphenol(s) and L-Arginine and Methods of Use Thereof

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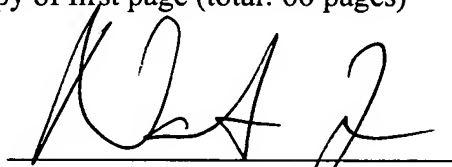
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Docket No. 1010/0102US4

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: Kati Chevaux *et al.*

Filed: 03/01/2004

Group Art Unit: 1655

Serial No: 10/790,289

Examiner: R. O. Winston

For: PRODUCTS CONTAINING POLYPHENOL(S) AND L-ARGININE AND METHODS  
OF USE THEREOF

**APPEAL BRIEF OF APPELLANT**

MAIL STOP: Appeal Brief-Patents  
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Sir:

This is an appeal from the Final Rejection mailed on August 8, 2007 and the Advisory action mailed on December 3, 2007 in which the Examiner finally rejected claims 31-74. The Notice of Appeal for this case was filed on December 07, 2007.

The Commissioner is authorized to charge the Appeal Brief filing fee of \$510.00 (under 37 CFR 41.20(b)(2)) and any additional fee or credit overpayment in connection with this communication to the **Deposit Account No. 50-2549**. A duplicate copy of this sheet is enclosed.

Table of contents of the Appeal Brief is on page 2. Page numbers for each of the items included in the brief is shown in the table of contents.

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**1. REAL PARTY IN INTEREST (37 CFR 41.37 (c)(1) (i))**

The patent application in the case appealed is owned by Mars, Incorporated, who is the real party of interest.

**2. RELATED APPEALS AND INTERFERENCES (37 CFR 41.37 (c)(1)(ii))**

There are no other related appeals or interferences known to appellant, assignee, or appellant's legal representative.

**3. STATUS OF CLAIMS (37 CFR 41.37 (c)(1)(iii))**

The status of claims on appeal is as follows:

Pending claims: 31-78

Claims appealed: 31-74

Withdrawn claims: 75-78

**4. STATUS OF AMENDMENTS (37 CFR 41.37 (c)(1)(iv))**

There have been no amendments filed in response to the final rejection.

## 5. SUMMARY OF CLAIMED SUBJECT MATTER (37 CFR 41.37 (c)(1)(v))

The independent claims on appeal are claims 31, 32, and 67. Each claim is reproduced below with references to the subject matter where it appears in the specification by page and line number.

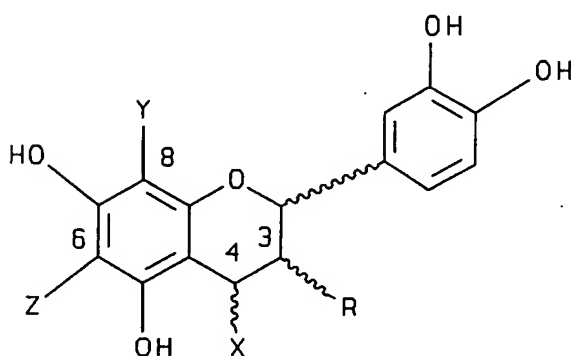
31. A non-chocolate food product comprising (i) a cocoa polyphenol and (ii) L-arginine in a combined amount effective to induce a physiological increase in nitric oxide upon ingestion by a human or a veterinary animal,

wherein the increase in nitric oxide has a therapeutic or prophylactic effect when the product is administered for an effective period of time, and the L-arginine is in the amount of at least 1mg/g;

with the proviso that when the cocoa polyphenol is in the form of a cocoa ingredient, the amount of L-arginine is greater than that provided with the cocoa ingredient.

[Reference to the Specification: *e.g.*, page 6, lines 1-20; page 7, lines 6-12; page 17, lines 19-24; page 21, lines 5-15; page 24, line 30-page 25, line 17].

32. A non-chocolate food product comprising (i) a polyphenol compound of formula A<sub>n</sub>, wherein n is 1 or 2 to 18 and A has the following formula:



R is 3-( $\alpha$ ) - OH, 3-( $\beta$ ), 3-( $\alpha$ )- O-saccharide, 3-( $\beta$ )-O-saccharide, 3-( $\alpha$ )-O-C(O)-R', or 3-( $\beta$ )-OC (O)-R';

bonding between adjacent monomers takes place at positions 4, 6 or 8;



a bond to a monomer in position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of A, hydrogen, and a saccharide moiety, with the proviso that as to at least one terminal monomer, bonding of the adjacent monomer thereto is at position 4 and optionally Y = Z = hydrogen; and

wherein the saccharide moiety is a mono- or di-saccharide moiety and may be optionally substituted with a phenolic moiety and R' may be an aryl or heteroaryl moiety optionally substituted with at least one hydroxyl group; and

salts, derivatives and oxidation products thereof;

and (ii) L-arginine in a combined amount effective to induce a physiological increase in nitric oxide upon ingestion by a human or a veterinary animal,

wherein the increase in nitric oxide has a therapeutic or prophylactic effect when the product is administered for an effective period of time, and the L-arginine is in the amount of at least 1mg/g;

with the proviso that when the polyphenol compound is in the form of a cocoa ingredient, the amount of L-arginine is greater than that provided with the cocoa ingredient.

[Reference to the Specification: *e.g.*, page 6, lines 1-23; page 7, lines 6-12; page 13, lines 4-23; page 17 lines, 1-6 and lines 19-24; page 21, lines 5-25; page 24, line 30-page 25, line 17].

67. A non-chocolate food product comprising a cocoa polyphenol in the amount of at least 1 mg/g and L-arginine in the amount of least 10 mg/g.

[Reference to the Specification: *e.g.*, page 24, line 30-page 25, line 4; page 25, lines 14-17].

**6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (37 CFR 41.37 (c)(1)(vi))**

1. Are claims 31-74 patentable over Romanczyk, Jr. (US 5,554,645) in view of Wideman *et al.* (US 6,127,421) under 35 USC Section 103?

7. **ARGUMENT (37 CFR 41.37 (c)(1)(vii))**

Rejection under 35 USC 103 over Romanczyk and Wideman

Claims 31-74 stand rejected under 35 USC 103 on the grounds that they are obvious over Romanczyk, Jr. (US 5,554,645; hereinafter referred to as ‘Romanczyk’) in view of Wideman *et al.* (US 6,127,421; hereinafter referred to as ‘Wideman’). The Examiner states that it would have been obvious to a person of skill in the art to modify the food composition of Romanczyk (which contains procyanidins) to include the other active ingredient (arginine) as taught by Wideman and arrive at the compositions recited in Appellants’ claims 31-74 because both procyanidins and L-arginine are taught to be useful for the same purpose, *i.e.*, anti-tumor purpose. The rejection should be reversed for the reasons shown below.

1. Claims 31-74 are patentable because of conflicting teachings of the prior art

The primary focus and teaching of Wideman is the use of L-arginine in chicken eggs for treatment/prevention of pulmonary hypertension syndrome in birds (*see*, entire patent). Regarding the teachings in Wideman of anti-tumor utilities, the Examiner refers to a background citation therein of Taylor *et al.* 1992 and the statement that dietary administration of L-arginine to chicken reduces tumor growth.

However, as of the effective filing date of the above Application, the knowledge in the art as to the anti-tumor effect of dietary arginine supplementation in mammals was controversial and contradictory reports existed in the field. On May 9, 2007, with their Response, Appellants submitted to the Patent Office a publication discussing the effects of arginine on tumor growth—Yeatman T. J. *et al.* Depletion of Dietary Arginine Inhibits Growth of Metastatic Tumor, *Arch. Surg.* 1991, 126(11):1376-82 (additional copy attached for the Examiner’s convenience) [hereinafter Yeatman].

At the outset, Yeatman refers to 70 years of investigation of the effects of arginine on tumor growth and states that “[d]espite these efforts, the effect of dietary arginine on tumor growth [had] not been clearly elucidates” and that arginine was shown to both stimulate and inhibit tumor growth (Yeatman, page 1376, col. 1, 1<sup>st</sup> par.). Yeatman then

goes on to show in a mouse (mammalian) model that dietary arginine depletion inhibited the growth of liver metastases of colorectal cancer cells (*see* Yeatman, entire article, *e.g.* Figs. 2-3). In contrast, arginine supplementation increased the weight of the tumors in comparison to control (Yeatman, page 1377, col. 2, last par.-1378, col. 1, 1<sup>st</sup> par., Fig 1).

Thus, Yeatman contains conflicting teaching to the teaching of Wideman cited by the Patent Office. It is well established that “prior art must be considered in its entirety, including disclosures that teach away from the claims” MPEP, Section 2141.02 VI. “When prior art contains apparently conflicting references, the [Office] must weigh *each* reference for its power to suggest solutions to an artisan of ordinary skill.” *In re Young*, 927 F.2d 588, 591; 18 U.S.P.Q.2d 1089 (Fed. Cir. 1991) (emphasis added) (copy attached). “Where the prior art contains ‘apparently conflicting’ teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered.” *Medichem v. Rolabo*, 437 F.3d. 1157, 1165; 77 U.S.P.Q.2d (Fed. Cir. 2006) (citing *In re Young*) (copy attached).

In the present case, the Examiner has failed to give consideration to the teachings of Yeatman. No analysis of Yeatman can be found in the “final” Official Action mailed August 8, 2007, nor is there any reasoning or explanation why a person of skill in the art would not have given weight to Yeatman’s teaching. In *In re Young*, Federal Circuit Court affirmed the Board’s finding which dismissed the conflicting reference and upheld the rejection because the Board analyzed the conflicting reference and correctly explained why the reference was not sufficient to discredit the teachings of the cited reference. *In re Young*, 927 F.2d at 591-592. This is not the case here. The Examiner has not met his burden.

In fact, a person of skill in the art, having both Wideman and Yeatman before her, would have had no motivation to combine the procyanidin of Romanczyk and L-arginine of Wideman with any reasonable expectation of success that an anti-tumor composition with two active ingredients could have been achieved. This is not an obvious to try situation discussed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. \_\_\_, 82 USPQ2d 1385 (2007) because the results of such a combination were

unpredictable. To arrive at the present invention, a person of skill in the art would have had to unduly experiment -this supports the finding of non-obviousness.

Reversal of the rejection of claims 31-74 is respectfully requested.

2. Claims 31-34, 41-53, 59-60 and 66 are patentable because the cited prior art fails to suggest all claimed limitations

Further to the arguments presented under subheading 1 above, claims 31-34, 41-53, 59-60, and 66 are patentable for an additional reason.

Claims 31-34, 41-53, 59-60, and 66 recite a non-chocolate food composition containing polyphenols and L-arginine “in an *amount effective* to induce a physiological increase in nitric oxide” (emphasis added). The effective amount limitation is a functional limitation which together with a numerical limitation for the amount of L-arginine structurally defines the scope of the claims, *i.e.*, it defines the amount of the compounds required to be present in the non-chocolate composition.

The Examiner rejects these claims and argues that the claimed amount is “merely a matter of judicious selection and routine optimization” (“final” Official Action, text spanning pages 3-4).

The Examiner has erred in applying the law of “routine optimization.” “[T]he rule [is] that discovery of an optimum value of a result-effective variable in a known process [or composition] is ordinarily within the skill in the art” *In re Boesch*, 617 F.2d 272, 276; 205 U.S.P.Q.2D 215 (CCPA 1980); *In re Antonie*, 559 F.2d 618; 195 U.S.P.Q. 6 (CCPA 1977); *Ex parte Buzzoni*, (Bd Pat Appl, January 30, 2008, appeal 2007-3725) (copies attached). “A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.” MPEP Section 2144.05 II B. Consequently, in order to make the claimed compositions obvious, Romanczyk and Wideman should have recognized that procyanidin of Romanczyk and arginine of Wideman are effective for increasing nitric

oxide (NO) (rather than for anti-tumor effects). In other words, procyanidin of Romanczyk and arginine of Wideman cannot be optimized for NO effects when such effects are not suggested by the cited prior art.

This is because “the prior art [must] have suggested ‘the kind of experimentation necessary to achieve the claimed composition’” *In re Boesch*, 617 F.2d at 276 (holding that such a showing was made). *See also, In re Antonie*, 559 F.2d at 620 (holding that such a showing was not made). In *In re Antonie*, the claims at issue recited a wastewater treatment device comprising a tank having certain “treatment capacity” which capacity was a function of “tank volume.” The prior art cited by the Patent Office disclosed the basic structure of Antonie’s device but was silent regarding the “tank volume.” The Court reversed the rejection because the cited prior art “was not trying to maximize or control ‘treatment capacity’;” “experiments suggested by [the cited art did] not reveal the property which applicant [had] discovered;” and “there [was] no evidence in the record that the prior art recognized that particular parameter affected the result.” *Id.*

Following the reasoning in *Antonie* and *Boesch*, Romanczyk and Wideman should have suggested to a person of skill in the art nitric oxide effects of their compounds before the experiments to optimize the amount of these compounds to achieve the nitric oxide effect could have been conducted. In the absence of such a recognized result, arriving at the amount limitations of Appellants’ claims 31-34, 41-53, 59-60, and 66 would have amounted to undue not routine optimization.

This conclusion is further supported by the above cited recent decision of the USPTO Board of Appeals and Interferences, which is also on point. In *Ex parte Buzoni*, the Appellant claimed an anchorless wheel bumper block (to be used as a stop in a parking facility), and the cited prior art disclosed a cellular arresting block (for use as a stop for aircrafts, trucks and other vehicles). The prior art block was larger than the claimed block and the Examiner rejected the claims on the ground that it would have required routine optimization to modify the block of the prior art and arrive at the claimed block. The Board disagreed and held that the Examiner failed to establish a *prima facie* case of obviousness because he failed to establish that an optimum obtained for the cited prior art block would have also been an optimum for the Appellants’ block.

Applying the Board's holding to the facts here, even if the Examiner had established that it would have been obvious to optimize the amounts of Romanczyk's and Wideman's compounds for anti-tumor purposes; the Examiner has failed to establish (and could not have as shown above) that it would have been obvious to optimize the amounts of the compounds to those recited in claims 31-34, 41-53, 59-60 and 66. *Prima facie* case of obviousness has not been met.

Reversal of the rejection 31-34, 41-53, 59-60 and 66 is believed to be in order and is respectfully requested.

3. Claims 35-40, 54-58, and 61-65 are patentable because the cited prior art fails to suggest all claimed limitations

Further to the arguments presented under subheading 1 above, claims 35-40, 54-58, and 61-65 are patentable for an additional reason.

Claims 35-40, 54-58, and 61-65 recite a non-chocolate food composition containing polyphenols and L-arginine "in an *amount effective* to induce a physiological increase in nitric oxide" (emphasis added) and further recite numeric limitations for both polyphenol and L-arginine. The Examiner argues that these claimed amounts can be routinely optimized.

Claims 35-40, 54-58, and 61-65 are patentable for the reasons shown under subheading 2 above, and further because explicit numeric limitations for the polyphenol are nowhere suggested by the combined teachings of Romanczyk and Wideman.

Reversal of the rejection of claims 35-40, 54-58, and 61-65 is believed to be in order and is respectfully requested.

4. Claims 67-74 are patentable because the cited prior art fails to suggest all claimed limitations

Further to the arguments presented under subheading 1 above, claims 67-74 are patentable for an additional reason.

Claims 67-74 recite a non-chocolate food composition containing cocoa polyphenol and L-arginine in certain numeric amounts (which amounts achieve physiologically relevant NO effects). The Examiner argues that the amounts can be routinely optimized. Claims 67-74 are patentable for the reasons shown under subheading 2 above, and further because explicit numeric limitations for polyphenol and L-arginine are nowhere suggested by the combined teachings of Romanczyk and Wideman.

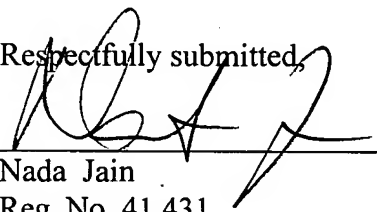
Reversal of the rejection of claims 67-74 is believed to be in order and is respectfully requested.

## CONCLUSION

In view of the above arguments, Appellants respectfully request reversal of the rejection of claims 31-74.

Date: February 7, 2008

Respectfully submitted,

  
\_\_\_\_\_  
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8. CLAIMS APPENDIX (37 CFR 41.37 (c)(1)(viii))

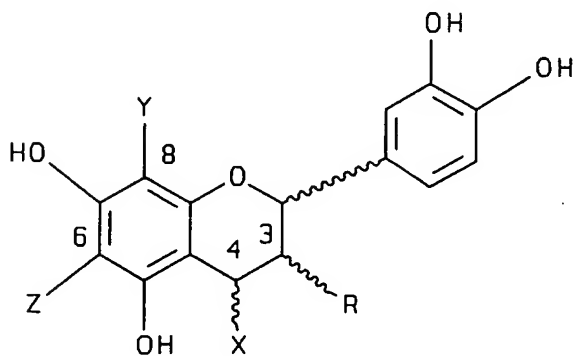
1-30. (canceled)

31. A non-chocolate food product comprising (i) a cocoa polyphenol and (ii) L-arginine in a combined amount effective to induce a physiological increase in nitric oxide upon ingestion by a human or a veterinary animal,

wherein the increase in nitric oxide has a therapeutic or prophylactic effect when the product is administered for an effective period of time, and the L-arginine is in the amount of at least 1mg/g;

with the proviso that when the cocoa polyphenol is in the form of a cocoa ingredient, the amount of L-arginine is greater than that provided with the cocoa ingredient.

32. A non-chocolate food product comprising (i) a polyphenol compound of formula  $A_n$ , wherein n is 1 or 2 to 18 and A has the following formula:



R is 3-( $\alpha$ ) - OH, 3-( $\beta$ ), 3-( $\alpha$ )- O-saccharide, 3-( $\beta$ )-O-saccharide, 3-( $\alpha$ )-O-C(O)-R', or 3-( $\beta$ )-OC (O)-R';

bonding between adjacent monomers takes place at positions 4, 6 or 8;

a bond to a monomer in position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of A, hydrogen, and a saccharide moiety, with the proviso that as to at least one terminal monomer, bonding of the adjacent monomer thereto is at position 4 and optionally Y = Z = hydrogen; and

wherein the saccharide moiety is a mono- or di-saccharide moiety and may be optionally substituted with a phenolic moiety and R' may be an aryl or heteroaryl moiety optionally substituted with at least one hydroxyl group; and

salts, derivatives and oxidation products thereof;

and (ii) L-arginine in a combined amount effective to induce a physiological increase in nitric oxide upon ingestion by a human or a veterinary animal,

wherein the increase in nitric oxide has a therapeutic or prophylactic effect when the product is administered for an effective period of time, and the L-arginine is in the amount of at least 1 mg/g;

with the proviso that when the polyphenol compound is in the form of a cocoa ingredient, the amount of L-arginine is greater than that provided with the cocoa ingredient.

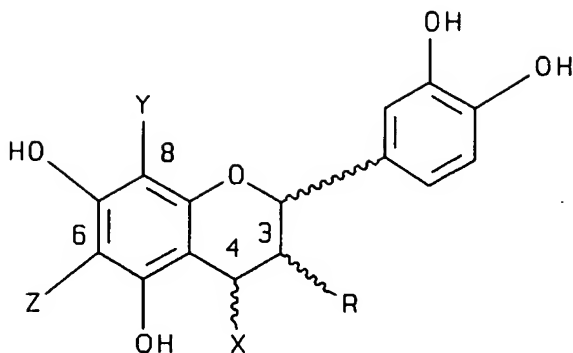
33. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the form of a cocoa extract.
34. The non-chocolate food product of claim 32, wherein the cocoa polyphenol is in the form of a cocoa extract.
35. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the amount of at least 1 mg/g.
36. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the amount of at least 1.25 mg/g.
37. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the amount of at least 1.5 mg/g.

38. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the amount of at least 2 mg/g.
39. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the amount of at least 5 mg/g.
40. The non-chocolate food product of claim 31, wherein the L-arginine is the amount of at least 10 mg/g.
41. The non-chocolate food product of claim 32, wherein the L-arginine is the amount of at least 10 mg/g.
42. The non-chocolate food product of claim 31, wherein the cocoa polyphenol is in the form of a cocoa ingredient.
43. The non-chocolate food product of claim 32, wherein the polyphenol compound is in the form of a cocoa ingredient.
44. The non-chocolate food product of claim 31, which is a peanut-based food product.
45. The non-chocolate food product of claim 44, wherein the peanut-based food product is peanut butter.
46. The non-chocolate food product of claim 44, wherein the peanut-based food product is peanut brittle.
47. The non-chocolate food product of claim 32, which is a peanut-based food product.

48. The non-chocolate food product of claim 47, wherein the peanut-based food product is peanut butter.
49. The non-chocolate food product of claim 47, wherein the peanut-based food product is peanut brittle.
50. The non-chocolate food product of claim 31, wherein the L-arginine is in the form of an L-arginine-containing ingredient selected from the group consisting of peanuts, walnuts, hazelnuts, almonds, and soy beans.
51. The non-chocolate food product of claim 32, wherein the L-arginine is in the form of an L-arginine-containing ingredient selected from the group consisting of peanuts, walnuts, hazelnuts, almonds, and soy beans.
52. The non-chocolate food product of claim 31, wherein the food product is a pet food.
53. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the form of cocoa extract.
54. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the amount of at least 1 mg/g.
55. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the amount of at least 1.25 mg/g.
56. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the amount of at least 1.5 mg/g.
57. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the amount of at least 2 mg/g.

58. The non-chocolate food product of claim 52, wherein the cocoa polyphenol is in the amount of at least 5 mg/g.
59. The non-chocolate food product of claim 52, wherein the amount of L-arginine is at least 10 mg/g.
60. The non-chocolate food product of claim 32, wherein the food product is a pet food.
61. The non-chocolate food product of claim 60, wherein the polyphenol compound is in the amount of at least 1 mg/g.
62. The non-chocolate food product of claim 60, wherein the polyphenol compound is in the amount of at least 1.25 mg/g.
63. The non-chocolate food product of claim 60, wherein the polyphenol compound is in the amount of at least 1.5 mg/g.
64. The non-chocolate food product of claim 60, wherein the polyphenol compound is in the amount of at least 2 mg/g.
65. The non-chocolate food product of claim 60, wherein the polyphenol compound is in the amount of at least 5 mg/g.
66. The non-chocolate food product of claim 60, wherein the amount of L-arginine is at least 10 mg/g.
67. A non-chocolate food product comprising a cocoa polyphenol in the amount of at least 1 mg/g and L-arginine in the amount of least 10 mg/g.

68. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 1.25 mg/g.
69. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 1.5 mg/g.
70. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 2 mg/g.
71. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 3 mg/g.
72. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 4 mg/g.
73. The non-chocolate food product of claim 67, wherein the cocoa polyphenol is in the amount of at least 5 mg/g.
74. The non-chocolate food product of claim 67, wherein L-arginine is in the amount of at least 100 mg/g.
75. (withdrawn) A method of treating or preventing an NO-responsive disease or disorder by administering to a subject in need thereof an effective amount of a composition comprising (i) a polyphenol compound of formula  $A_n$ , wherein n is 1 or 2 to 18 and A has the following formula:



R is 3-( $\alpha$ ) - OH, 3-( $\beta$ ), 3-( $\alpha$ )- O-saccharide, 3-( $\beta$ )-O-saccharide, 3-( $\alpha$ )-O-C(O)-R', or 3-( $\beta$ )-OC (O)-R';

bonding between adjacent monomers takes place at positions 4, 6 or 8;

a bond to a monomer in position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of A, hydrogen, and a saccharide moiety, with the proviso that as to at least one terminal monomer, bonding of the adjacent monomer thereto is at position 4 and optionally Y = Z = hydrogen; and

wherein the saccharide moiety is a mono- or di-saccharide moiety and may be optionally substituted with a phenolic moiety and R' may be an aryl or heteroaryl moiety optionally substituted with at least one hydroxyl group; and

salts, derivatives and oxidation products thereof;

and (ii) L-arginine in a combined amount effective to modulate nitric oxide and/or NO synthase upon ingestion by a human or a veterinary animal,

wherein the L-arginine is in the amount of at least 1mg/g;

with the proviso that when the compound is in the form of a cocoa ingredient, the amount of L-arginine is greater than that provided with a cocoa ingredient.

76. (withdrawn) The method of claim 75, wherein the NO-responsive disease and/or disorder is selected from the group consisting of: hypertension, cardiovascular disease, renal disease, and impaired cognitive function.

77. (withdrawn) The method of claim 76, wherein the composition is a food.

78. (withdrawn) The method of claim 76, wherein the composition is a pharmaceutical.



**9. EVIDENCE APPENDIX (37 CFR 41.37 (c)(1)(ix))**

**I. Journal publications:**

1. *Yeatman, T. J., Risley G. L., and Brunston, M. E.*, Depletion of Dietary Arginine Inhibits Growth of Metastatic Tumor, Archives of Surgery, 1991, Volume 126, Number 11, pages 1376-1381. (total: 6 pages)

**II. Case Law:**

1. *In re Antonie*, 559 F.2d 618; 195 U.S.P.Q. 6 (CCPA 1977). (total: 3 pages)
2. *In re Boesch*, 617 F.2d 272; 205 U.S.P.Q. 215 (CCPA 1980). (total: 7 pages)
3. *Ex Parte Buzzoni*, (Board of Patent Appeals and Interferences, January 30, 2008, Appeal 2007-3725). (total: 10 pages)
4. *Medichem, S. A. v. Rolabo, S. L.*, 437 F.3d 1157; 77 U.S.P.Q.2D 1865 (Fed. Cir. 2006). (total: 10 pages)
5. *In re Young*, 927 F.2d 588; 18 U.S.P.Q.2D 1089 (Fed. Cir. 1991) (total: 4 pages)

# Depletion of Dietary Arginine Inhibits Growth of Metastatic Tumor

Timothy J. Yeatman, MD; Geoffrey L. Risley, MD; Mathew E. Brunson, MD

• The effects of dietary arginine on the growth of a murine colon tumor metastatic to the liver were examined in a model of advanced neoplastic disease. Tumor growth was influenced by arginine both in vivo and in vitro. An arginine-supplemented diet stimulated tumor growth by 55% compared with controls. Conversely, an arginine-depleted diet inhibited tumor growth by 78% compared with controls. In vitro culture of both murine and human colon tumor cells confirmed that arginine was necessary for cell growth. Flow-cytometric analysis using propidium iodide and bromodeoxyuridine suggested that colon tumor cells cultured without arginine enter a quiescent S phase and depend on arginine for further growth and cell cycle progression. The potential roles for selective dietary arginine modulation in patients with cancer with advanced disease are discussed.

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The influence of arginine on tumor growth and host nutrition has been investigated for more than 70 years.<sup>1</sup> Despite these efforts, the effect of dietary arginine on tumor growth has not been clearly elucidated. In some systems, arginine has been shown to stimulate tumor growth,<sup>2,3</sup> while in other models, inhibition of tumor growth was noted.<sup>5,8</sup> This apparent paradox may be explained by the concept that in vivo tumor growth is influenced by multiple, competing factors.

It has been postulated that tumor growth is a dynamic process involving a "predator-prey" competition between immunocompetent cells and neoplastic cells in which growth is the vector sum of cell destruction and cell proliferation.<sup>9</sup> In this model, tumor progression depends on the capacity of the immune system to recognize and destroy neoplastic cells—a capacity that may be related to the degree of tumor immunogenicity. Recent reports have suggested that

arginine-supplementation may suppress the growth of immunogenic tumors because of host immunostimulatory effects; however, these growth-inhibiting effects were not seen with tumors that were weakly immunogenic. Growth may occur in this system because weakly immunogenic tumor cells escape recognition and destruction by otherwise effective tumor-directed immune responses.<sup>5,10-12</sup>

Using a weakly immunogenic colon cancer model, we determined the effects of arginine on tumor growth. Because arginine is considered essential for in vitro cell culture of both normal and neoplastic cells, we hypothesized that in vivo tumor propagation may depend on dietary arginine and that arginine depletion could inhibit tumor growth. Likewise, because immune defenses directed against weakly immunogenic tumor may not effectively compete with cell proliferation, arginine supplementation might enhance tumor growth.

We chose a model of experimental liver metastasis that simulates a state of advanced neoplastic disease in which nutritional deficits may become clinically relevant. The effects of both dietary arginine supplementation and dietary arginine depletion on the subsequent in vivo growth of liver metastases were examined. Similarly, the effects of arginine depletion and repletion on the propagation of these tumor cells in vitro were investigated.

## MATERIALS AND METHODS

### Animals

Six- to eight-week-old BALB/c mice were obtained from the Jackson Laboratory (Bar Harbor, Me) and housed in the Department of Pathology, Tumor Biology Mouse Colony, University of Florida, Gainesville. Mice had free access to solid chow and water and five mice were housed per cage. The mice were age, weight, and sex matched for each experiment.

### Cell Lines and Routine Culture Conditions

Cell line CT-26 was originally derived from a chemically induced primary, undifferentiated murine colorectal adenocarcinoma and was syngeneic with the BALB/c murine strain. The cells are known to be weakly immunogenic (as measured with challenge and rechallenge experiments) but highly tumorigenic.<sup>13</sup> Cells were routinely cultured in vitro as a monolayer at 37°C in a humidified incubator containing 7% carbon dioxide in air. Cells were grown in minimal essential medium (Grand Island Biologicals, Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum (Grand Island Biologicals) at  $5 \times 10^5$  cells per 10 mL. Near confluence, after 4 days of growth, cell monolayers were detached from the Petri dish (No. 3100,

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Costar, Cambridge, Mass) after a 3-minute incubation at room temperature with 0.7-mmol/L ethylenediaminetetraacetic acid in phosphate-buffered saline, which did not contain calcium or magnesium, supplemented with 0.6-mmol/L glucose and subcultured in fresh medium. Cell viability was determined with trypan blue dye exclusion using a hemocytometer.

Human colon adenocarcinoma cells (HT-29) were obtained from the American Type Tissue Culture Collection (Rockville, Md) and cultured as a monolayer (applying standard conditions explained above) in RPMI medium (Grand Island Biologicals) with 10% fetal bovine serum.

#### Experimental Metastasis Assay

Experimental liver metastases were produced in vivo using intrasplenic injection. Mice were anesthetized before intrasplenic injection with an intraperitoneal injection of 3 mg of ketamine hydrochloride and 0.03 mg of acepromazine maleate in phosphate-buffered saline. A suspension of  $1.25 \times 10^5$  to  $2.5 \times 10^5$  tumor cells in 0.5 mL of phosphate-buffered saline was injected into the inferior splenic pole over approximately 1 minute using a controlled-rate infusion syringe pump (No. 355, Sage Inc, Cambridge, Mass). A small hemoclip was then applied to the inferior splenic pole to prevent hemorrhage and back-diffusion of tumor cells into the free peritoneal cavity. Surgical incisions were closed with metal clips. Splenectomy was not performed. Mice underwent necropsy on day 14, and the extent of hepatic and other metastases was recorded. Mice received an intravenous injection of 10% india ink before necropsy to aid in detection of hepatic metastases. Livers were excised and immediately weighed.

#### Murine Diets

**Standard Chow.**—To examine the effects of supplemental arginine, mice were fed with standard solid mouse chow (23.4% protein and 1.38% arginine) ad libitum and were randomly assigned to one of two groups. Mice were permitted to drink water supplemented with 1% arginine hydrochloride or 1.7% (isonitrogenous) glycine ad libitum. Mice were administered supplemented water 7 days before tumor cell inoculation. Solid chow and water intake were monitored in each group.

**Amino Acid-Defined Diets.**—To examine the effects of dietary arginine depletion, mice were randomly assigned to be fed ad libitum one of two solid chow, amino acid-defined diets: standard-content, arginine-repleted diet (1.2% arginine) or arginine-depleted diet (no arginine). The arginine-depleted diet provided only 0.32% less nitrogen than the arginine-repleted diet. Water without any additives was administered ad libitum. These specific diets were prepared by Teklad Research Diets (Madison, Wis). Specific dietary formulas are listed in Table 1. All mice were placed on the appropriate diet 7 days before tumor cell injections. Solid chow and water intake were monitored for each group.

#### Culture Conditions Before DNA Analysis

Select-amine kits (Grand Island Biologicals) were used to formulate arginine-depleted or arginine-repleted minimal essential medium and RPMI medium. In vitro tumor growth was analyzed with flow cytometry after culture of  $5 \times 10^5$  CT-26 tumor cells in 10 mL of minimal essential medium or  $5 \times 10^5$  HT-29 tumor cells in 10 mL of RPMI. CT-26 cells were cultured without or with (0.013% [0.59 mmol/L]) supplemented arginine. HT-29 cells were cultured in multiple arginine concentrations ranging from none to 1.14 mmol/L. Cultures were harvested after 4 days.

#### Flow Cytometry

**DNA Analysis With Propidium Iodide.**—After culture in which specific media conditions were applied, cells were harvested and counted using a hemocytometer. Cells were then fixed in 70% ethanol solution and treated with 10  $\mu$ g of propidium iodide (PI; Sigma Chemical Corp, St Louis, Mo), per milliliter of solution, 0.5% polysorbate 20, and 400 U ribonuclease I (Sigma)

Table 1.—Composition of Amino Acids in Arginine-Repleted, Defined Diet

Amino Acid	Amount, g/kg
Alanine	3.5
Arginine*	12.1
Asparagine	6.0
Aspartic acid	3.5
Cystine	3.5
Glutamic acid	40.0
Glycine	23.3
Histidine	4.5
Isoleucine	8.2
Leucine	11.1
Lysine	18.0
Methionine	8.2
Phenylalanine	7.5
Proline	3.5
Serine	3.5
Threonine	8.2
Tryptophan	1.8
Tyrosine	5.0
Valine	8.2

\*Omitted in composition of arginine-depleted diet.

before flow cytometric analysis using an argon laser (FAC-STAR, Becton-Dickinson, Oxnard Calif) with an excitation wavelength of 488 nm and a measured emission wavelength of  $515 \pm 20$  nm. Data were collected and analyzed using a computer program (Consort 30, Becton-Dickinson). DNA histograms were used to perform cell cycle analysis. The percentage of cells in each phase of the cell cycle (S, G2, and M) was determined in duplicate.

**DNA Analysis With PI and Bromodeoxyuridine.**—After culture of HT-29 cells in nonarginine and 0.07-mmol/L and 0.57-mmol/L arginine-repleted RPMI medium, 10 mmol/L of 5'-bromo-2'-deoxyuridine (BrdUrd) was added to selected cultures for 1 hour at 37°C. Cells were then fixed with ethanol and denatured with 4N hydrochloride with 0.5% trinitrotoluene (Triton-X 100, Sigma Chemical Corp). According to standardized procedures,<sup>14</sup> cells were then labeled with fluorescein isothiocyanate-conjugated anti-BrdUrd antibody (Becton Dickinson) followed by PI. Simultaneous red and green fluorescence was then measured as indexes of PI and BrdUrd incorporation, respectively.

#### Amino Acid Analysis

Analysis of amino acid in whole blood was performed by the Metabolic Assessment Laboratory of the University of Florida, Gainesville.

#### Statistical Analysis

Data regarding liver weights were expressed as means  $\pm$  SDs and analyzed for population differences by the two-tailed independent t test or by analysis of variance. Liver metastases were expressed as median values with associated ranges and analyzed with the Mann-Whitney U test.

#### RESULTS

##### Effect of Arginine Supplementation on the In Vivo Growth of Colorectal Liver Metastases

To determine the effect of the addition of arginine to the standard chow diet (which already contained 1.4% arginine), mice were randomly assigned to one of two groups before tumor cell inoculation. The first group was given water supplemented with 1% arginine hydrochloride ad libitum, whereas an isonitrogenous dose of 1.7% glycine was added to the water of the second group, which was allowed this water ad libitum. There was no significant difference between groups in water or chow intake. Similarly, although small splenic tumors were occasionally observed, splenic

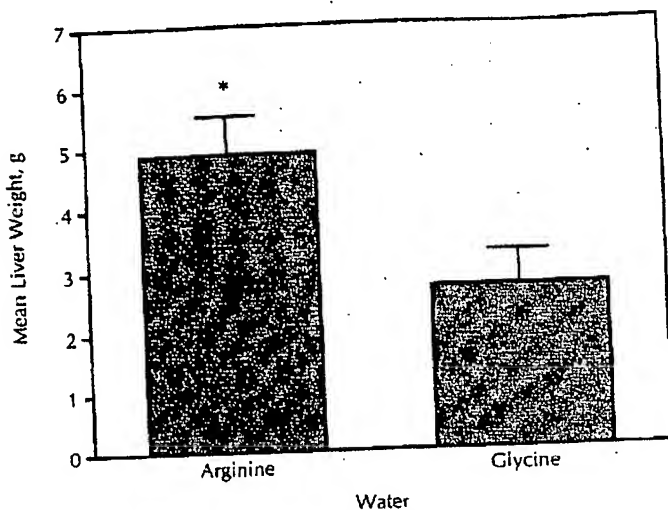


Fig 1.—Supplementation of water with 1% arginine ( $n=8$ ) vs supplementation with 1.7% glycine ( $n=10$ ) results in the stimulation of in vivo tumor growth (55% increase in weight; asterisk indicates  $P<.02$ ) in the liver. Data are mean liver weights  $\pm$  SEs.

weights between groups were not different.

Because metastases were confluent in both groups, livers were weighed as a measure of tumor burden with the finding that the mean liver weights for the group receiving water with arginine (4.9 g) were 55% greater ( $P<.02$ ) than the mean weights of the group receiving water with glycine (2.7 g) (Fig 1).

#### Effect of Arginine Depletion on the In Vivo Growth of Colorectal Liver Metastases

To confirm the growth-dependence of metastatic tumors on dietary arginine, a second method of dietary arginine manipulation was used. Mice were randomly assigned to two groups and fed either an arginine-depleted (nonarginine), amino acid-defined diet or a standard-content arginine diet (1.2% arginine). In this experiment, tumor inoculum was reduced to  $1.25 \times 10^5$  cells in 0.5 mL of phosphate-buffered saline to prevent confluence of metastatic foci. Again, no significant differences were noted between the two groups in water or chow intake or splenic weights. No splenic tumors were observed in these animals.

Arginine levels in whole blood were measured in animals ( $n=4$ ) randomly selected from both groups. Although there was a trend toward decreased arginine levels in animals fed nonarginine diets ( $0.117 \pm 19$  mmol/L) vs those fed arginine-repleted diets ( $0.154 \pm 18$  mmol/L), the difference was not significant ( $P=.10$ ).

When the median number of metastases were ascertained for each group, the arginine-depleted group was found to have 78% fewer (median, 46 metastases per animal) grossly visible metastatic nodules than the arginine-repleted group (median, 206 metastases per animal;  $P<.05$ ; Fig 2). The relative differences between the arginine-repleted and arginine-depleted groups can be seen in Fig 3. No significant differences were noted in liver weights between groups because of the smaller tumor burdens.

#### Effect of Arginine Depletion on Tumor Cell Growth In Vitro

Noting the apparent dependence of in vivo tumor growth on dietary arginine, the effects of arginine depletion and repletion were examined in vitro. CT-26 colon carcinoma cells ( $5 \times 10^5$ ) were cultured in duplicate in either depleted or repleted medium, with standard amounts of arginine (0.013%) being used in the latter. Nonarginine conditions essentially halted all cell growth, as evidenced by the retrieval (4 days after incubation) of  $2.4 \times 10^5$  fewer cells than the number added. When the cells were cultured in the presence of arginine, there were  $9 \times 10^5$  additional cells (total,  $1.4 \times 10^6$ ; Fig 4). Viability was greater than 98% in both the arginine repleted and the arginine-depleted groups.

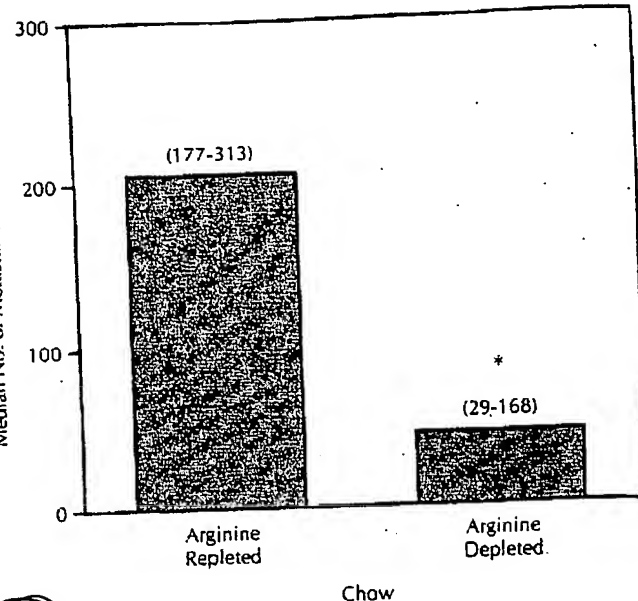


Fig 2.—Selective dietary depletion of arginine ( $n=8$ ) vs arginine repletion ( $n=10$ ) diminishes the growth of liver metastases by 78% (asterisk indicates  $P<.05$ ). Ranges of counts of tumor colonies in the liver are displayed in parentheses.

tion and repletion were examined in vitro. CT-26 colon carcinoma cells ( $5 \times 10^5$ ) were cultured in duplicate in either depleted or repleted medium, with standard amounts of arginine (0.013%) being used in the latter. Nonarginine conditions essentially halted all cell growth, as evidenced by the retrieval (4 days after incubation) of  $2.4 \times 10^5$  fewer cells than the number added. When the cells were cultured in the presence of arginine, there were  $9 \times 10^5$  additional cells (total,  $1.4 \times 10^6$ ; Fig 4). Viability was greater than 98% in both the arginine repleted and the arginine-depleted groups.

Flow cytometric analysis of DNA content/cell demonstrated that the difference between the groups might be secondary to effects on cell division. Growth-phase DNA analysis demonstrated that the percentage of cells in the S, G2, and M phases was significantly greater ( $P<.02$ ) in the nonarginine-treated cells (32.5%) than in the arginine-treated cells (22.0%), suggesting that growth and progression through the cell cycle depend on arginine (Fig 5).

Further study of this cell cycle aberration was performed using human colon adenocarcinoma cells (HT-29). Tumor cell growth was significantly—but reversibly—inhibited in a dose-dependent fashion by selective arginine depletion from culture medium (Table 2). Note that the effective dose range in vitro (0.07 to 0.14 mmol/L) closely approximates the in vivo levels in whole blood (0.12 to 0.15 mmol/L). While HT-29 cells in cultures containing 0.14 mmol/L arginine or higher concentrations were recovered in numbers approximately four times that inoculated, only 44% of inoculated HT-29 cells were recovered from the nonarginine cultures. An intermediate number of cells (1.45 times the number inoculated) were recovered in the 0.07-mmol/L arginine cultures. Inhibition of tumor growth was unabated despite the addition of isonitrogenous concentrations of glycine. Tumor cells initially cultured in nonarginine medium and later recultured in 0.57-mmol/L arginine multiplied (2.12 times the num-

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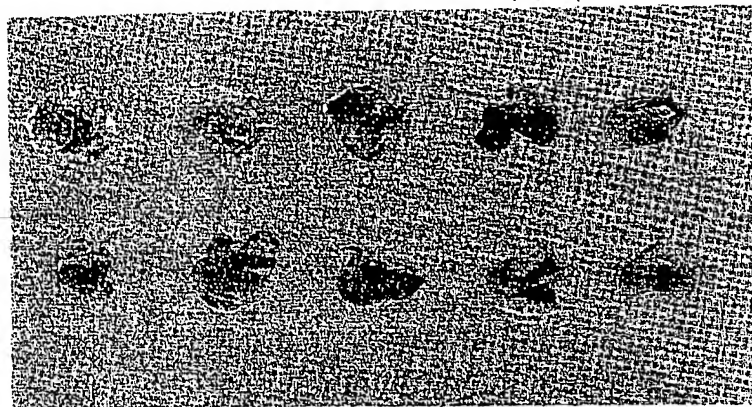
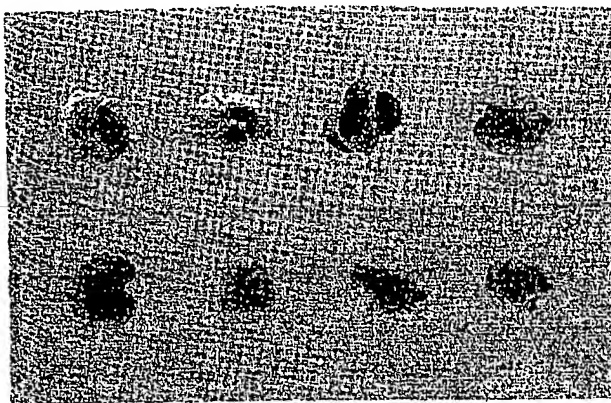


Fig 3.—Gross liver metastases that developed in the absence of (left) vs in the presence of (right) dietary arginine.

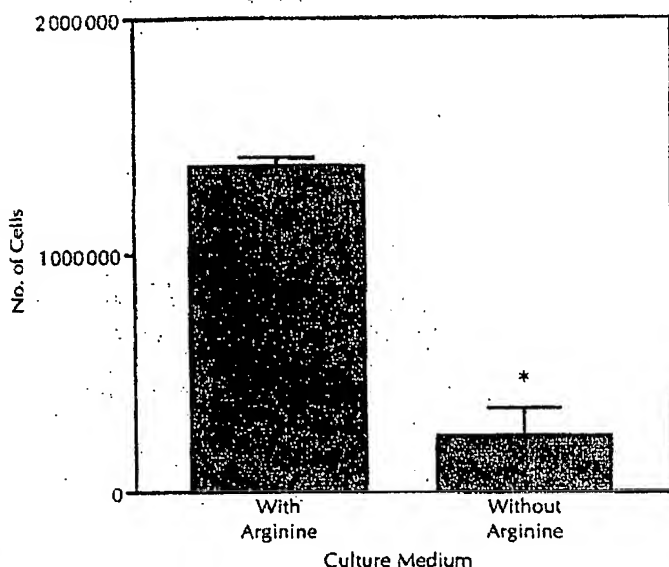


Fig 4.—Nonarginine cell culture medium results in less in vitro cell growth than does culture medium containing 0.013% arginine ( $n=2$ , asterisk indicates  $P<.02$ ). Data are means  $\pm$  SEs.

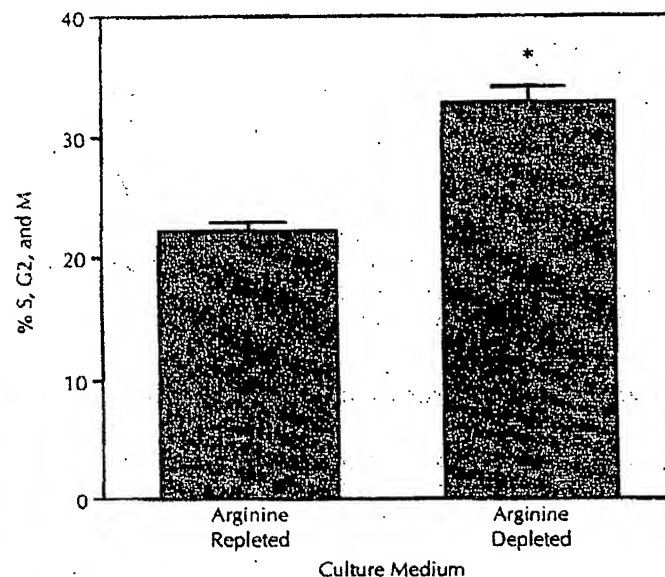


Fig 5.—Arginine depletion of cell culture medium in vitro, compared with arginine repletion, increases the percentage of cells in S, G2, and M phases of the cell cycle from 22.0% to 32.5% ( $n=2$ , asterisk indicates  $P<.02$ ).

ber of cells inoculated were recovered), suggesting that the effect of arginine depletion is reversible. Flow-cytometric DNA analysis confirmed a progressive increase in the number of S-phase cells with decreasing arginine concentrations (ranging from 24% for 0.57-mmol/L arginine to 43% in the absence of arginine).

To determine the nature of this S-phase accumulation, cells were labeled with PI alone (controls) or with PI and BrdUrd simultaneously (Fig 6). The abscissa represents linear relative red fluorescence due to PI staining of cell nuclei. The ordinate represents log scale relative to green fluorescence secondary to BrdUrd uptake. While PI labels all DNA, BrdUrd competes with thymidine and labels only newly synthesized DNA and can be detected with fluorescein-labeled anti-BrdUrd monoclonal antibody.<sup>15</sup> These studies demonstrate that not all cells accumulating in S phase are actually synthesizing DNA but, rather, are quiescent. While nearly all S-phase cells grown in 0.57-mmol/L arginine were labeled with BrdUrd (Fig 6, C), fewer cells and almost none were labeled with BrdUrd when cultured in 0.07-mmol/L arginine (Fig 6, B) and nonarginine medium (Fig 6, A), respectively.

## COMMENT

Using an advanced model of neoplastic disease, we found that dietary arginine depletion may reduce the growth of liver metastases. We also found that, using a weakly immunogenic tumor model, arginine supplementation may stimulate the growth of tumor in vivo.

Although the classic experiments of Rose et al<sup>16</sup> demonstrated that humans require only eight essential amino acids for nitrogen balance (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), Eagle<sup>17</sup> found that human and animal normal and neoplastic cells required additional amino acids for propagation in vitro. Arginine, cyst(e)ine, glutamine, histidine, and tyrosine were the additional amino acids identified. A number of theories have been proposed to explain why tumor can grow in vivo without the amino acids considered essential for in vitro culture conditions. One simplistic explanation is that the host may provide the arginine needed for tumor growth.

Despite some knowledge of the nature of amino acid growth requirements of tumor cells, both the role and mechanism of action of arginine in the tumor-host rela-



Table 2.—Dose-Dependent Effect of Arginine on Human Colon Cancer Growth In Vitro

	Arginine Concentration in Culture Medium, mmol/L*							
	None	0.07	0.14	0.29	0.57	1.14	4.50†	0.57‡
% cells recovered§	44	145	449	398	465	392	165	212
% G1-phase cells	47.9	51.6	None	None	59.5	None	None	53.6
% S-phase cells	43.3	33.9	None	None	24.4	None	None	35.6
% G2-phase and M-phase cells	8.9	14.5	None	None	16.1	None	None	10.8

\*Cells were cultured in various concentrations of arginine for 3 days before harvest.

†Cells cultured in isonitrogenous glycine (control medium).

‡Cells were initially cultured in nonarginine medium for 3 days, then recultured in 0.57-mmol/L arginine for 3 days before harvest.

§Number of cells recovered divided by the number of cells inoculated and multiplied by 100. Viability was greater than 98% as measured by propidium iodide staining for all groups.

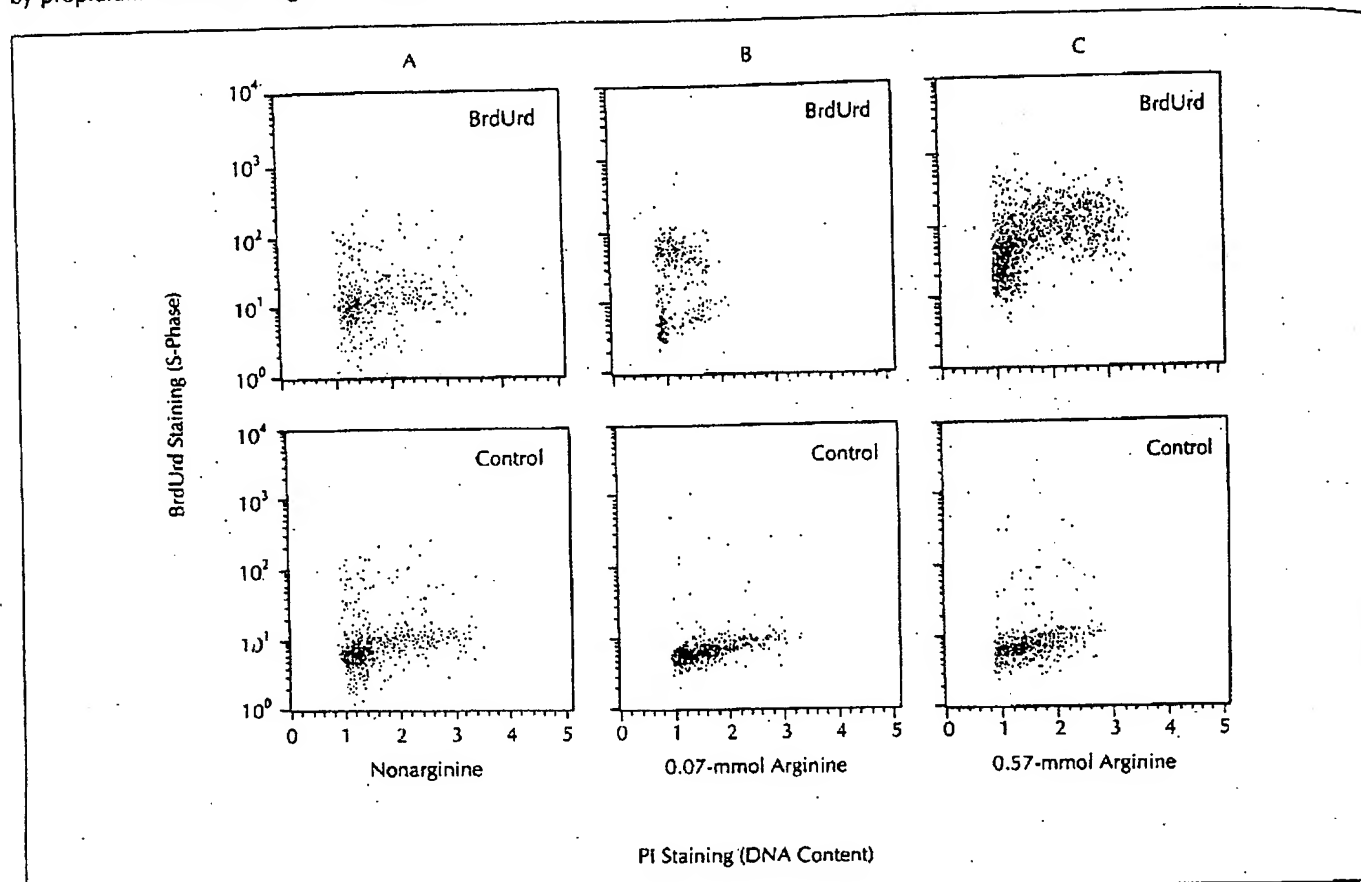


Fig. 6.—Propidium iodide (PI) and 5'-bromo-2'-deoxyuridine (BrdUrd)-labeled HT-29 cells. With arginine depletion (A and B), few S-phase cells (measured by PI uptake) synthesize DNA (measured by BrdUrd uptake), while most S-phase cells exposed to 0.57-mmol/L arginine (C) uptake BrdUrd.

tionship have not been elucidated. Although arginine appears to be an immunostimulant of cellular immunity in certain situations, it is not clear whether this effect applies only to immunogenic tumors. Reynolds et al<sup>5</sup> suggested that the antitumor effect of arginine may be mediated by arginine's modulation of host-tumor immune interaction, but only in tumors expressing immunogenic, tumor-associated antigens. In their model using protein-depleted mice, arginine suppressed the subcutaneous growth of moderately immunogenic tumor by enhancing cytotoxic T-lymphocyte development and natural killer cell activity while stimulating the growth of a poorly immunogenic clonal variant. Perhaps weakly immunogenic tumor escapes recognition and destruction by immune defenses—even when these defenses are augmented by supplemental arginine.

To define the effects of arginine on tumor growth (an issue separate from its potential immunostimulatory effects) we used a poorly immunogenic murine colon tumor with metastases introduced experimentally to the liver.<sup>13</sup> We hypothesized that in vivo tumor propagation might depend on the presence and quantity of arginine when propagation occurred while immune defenses may have been relatively ineffective. We chose a metastatic model of liver metastasis instead of the existing, common, subcutaneous-inoculation models because of its close approximation to human cancer progression.

We used two different in vivo experimental approaches, and the results of both experiments led us to the same conclusion: supplemented arginine enhances the growth of metastatic tumor cells, whereas its absence or deficiency inhibits growth. Differences in tumor growth

cannot be explained by the nutritional effects of arginine on liver mass. It has been reported<sup>10</sup> that supplementing water with arginine does not result in excessive changes in carcass weight compared with the carcass weight of control animals receiving water supplemented with glycine, and we found no differences in liver weights between the animals receiving arginine-depleted or arginine-repleted amino acid-defined diets. Differences in tumor growth appeared to be independent of nitrogen supplementation, as diets were isonitrogenous. Although these in vivo results could be interpreted as effects on tumor cell seeding efficiency (via effects on end-organ adhesion) rather than on the growth of tumor cells, we think this is unlikely because the tumor's growth dependence on arginine was also confirmed with in vitro experiments. There was no growth without arginine, but normal growth was observed when arginine was present in the medium. These results confirm that the original observations of Eagle<sup>17</sup> were also valid in our experimental model. This effect was similar for both murine (CT-26) and human (HT-29) colon tumor cell lines.

The apparent contradiction of a high S phase associated with lower but reversible growth rates in vitro is likely secondary to cells that have arrested in S<sub>0</sub> (the quiescent S phase)<sup>18</sup> and require arginine for complete cell cycle progression. Data from our experiments in which labeling of cells with PI and BrdUrd occurred simultaneously add supportive evidence to this hypothesis by demonstrating that a significant proportion of cells accumulating in the S phase secondary to arginine-depleted culture conditions are actually quiescent and do not synthesize DNA. Further study, perhaps using thymidine-pulse or 5-bromodeoxyuridine-pulse labeling,<sup>14</sup> is needed to determine the precise mechanism underlying these cell cycle aberrations.

These experimental findings suggest that metastatic tumor growth can be inhibited with dietary depletion of arginine. This decrease in tumor growth may be related to the basic tumor requirement of arginine for growth that was demonstrated in vitro and to the low level of tumor immunogenicity. Although this observation has yet to be made of cancer occurring in humans, potential clinical benefit might be obtained by using nonarginine hyperalimentation or amino acid-defined diets that may slow the growth of metastatic tumor. This concept is particularly relevant to humans in that most solid tumors are weakly immunogenic.

Additionally, because of the reversible nature of the in vitro accumulation of quiescent S-phase cells observed with arginine depletion, potential exists for the use of selective dietary arginine modulation (depletion followed by repletion) of cell cycle progression. For example, it might be possible to synchronize the growth of metastatic tumor cells in vivo and enhance the effectiveness of cell-cycle specific chemotherapy. Further studies examining the DNA from fresh tumor are needed to confirm this. Ultimately, we propose that arginine should not be considered "good" or "bad" for the tumor-bearing host, but, rather, viewed as a tool for modifying the biologic behavior characteristic of the tumor-host relationship.

We would like to thank David M. Ota, MD, for his thoughtful and constructive criticisms of this article and Philip Frost, MD, Departments of Cell Biology and Medicine, University of Texas, MD Anderson Cancer Center, Houston, for supplying the adenocarcinoma cells. We would also like to acknowledge the expert

assistance of Nguyen Van, MD, in performing flow cytometric analysis.

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## Discussion

DAVID M. OTA, MD, Houston, Tex: Have you looked at plasma arginine levels in your animals that were on the special diets? Please comment on a possible mechanism. Arginine seems to be an essential nutrient here. How do you think that impacts on the cell growth process within the tumor? Is it protein synthesis, or is it some other metabolic pathway for which arginine is essential for cell growth?

DAVID S. ROBINSON, MD, Miami, Fla: Can you tell us how those cells that escaped into G2 and M, still depleted of arginine, were allowed to get through? Then, with regard to the host, tell us about the remaining cellular tissues that are non-

559 F.2d 618, \*; 1977 CCPA LEXIS 118, \*\*;  
195 U.S.P.Q. (BNA) 6

LEXSEE 559 F.2D 618, 620

IN THE MATTER OF THE APPLICATION OF RONALD L. ANTONIE

Patent Appeal No. 76-681.

UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

559 F.2d 618; 1977 CCPA LEXIS 118; 195 U.S.P.Q. (BNA) 6

AUGUST 18, 1977, Decided

**PRIOR HISTORY:** [\*\*1] Serial No. 331, 796.

**COUNSEL:** Arthur H. Seidel, Thomas W. Ehrmann, Milwaukee, Wis. (Quarles & Brady, Milwaukee, Wis.), attorneys of record, for appellant.

Joseph F. Nakamura, Washington, D.C. for the Commissioner of Patents, R. D. Edmonds, Washington, D.C., of counsel.

**OPINION BY:** BALDWIN

**OPINION**

[\*618] BALDWIN, Judge.

This is an appeal from a decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of claims 1, 2 and 3 of an application for "Rotating Biological Contactor Apparatus" <sup>1</sup> as obvious under 35 USC 103 in view of El-Naggar. <sup>2</sup> We reverse.

1 Serial No. 331, 796, filed February 12, 1973.

2 Method of Treatment of Sewage by Bio-Oxidation and Apparatus Therefor," U.S. Patent No. 3,335,081, issued August 8, 1967.

**The Invention**

Appellant claims a wastewater treatment device in which wastewater is continuously passed through a tank. Semiimmersed contactors (disks) are continuously rotated to aerate their immersed portions and thereby to aerate both microorganisms that grow on the contactors and the wastewater itself. For this discussion, several variables are important in this device. "Throughput" is the volume [\*\*2] of wastewater per unit time (gal/day) which the device must treat. "Contactor area" is the total area of the contactors which is exposed to the wastewater as the contactors are rotated (sq. ft.). "Tank volume" is the actual volume of liquid in the tanks in which the

contactors [\*619] rotate (gal.). The ratio of throughput to contactor area (gal./day/sq. ft.) is called the "hydraulic loading." Two concepts of effectiveness of the equipment are important in this discussion. The primary prior art reference uses the term "efficiency" to denote the percent impurity reduction which a given set-up of the device achieves and we shall so use the term. Appellant uses the term "maximum treatment capacity" to denote when a unit of contactor area is providing maximum "efficiency" for a given "throughput" or maximum "throughput" for a given "efficiency." It is essential to understand the distinction between "efficiency," a matter of ultimate effectiveness independent of the efficiency of the equipment, and "treatment capacity," a matter of the efficiency or effectiveness of a unit of contactor area. The latter is more properly associated with the normal use of the term "efficiency" denoting [\*\*3] maximum result from a limited resource.

Appellant's claimed device has a ratio of tank volume to contactor area of 0.12 gal./sq. ft. <sup>3</sup> Appellant maintains that this ratio is the most desirable or optimum for all set-ups of the device in the sense that using a lower value gives lower "treatment capacity" and using a greater value gives no increase in "treatment capacity," merely increasing costs. Thus, the value is optimum in that it maximizes "treatment capacity" so that the effectiveness of a given contactor is maximized.

3 Claims 1 and 2 recite "at least about 0.12" while claim 3 recites "about 0.12."

**The Prior Art**

El-Naggar teaches the basic structure of the device claimed by appellant but is silent regarding quantitative design parameters other than to give data on a single example, which data was apparently complete except for any discussion of "tank volume." El-Naggar stated the "efficiency" (obviously referring to the purity of the output) could be increased to 95% by increasing the area of the contactor.

**The Rejection**



The examiner rejected the claims as obvious under 35 USC 103, noting that the basic device in question is old as taught by El-Naggar. [\*\*4] While the ratio of tank volume to contactor area of 0.12 gal./sq. ft. is not disclosed in El-Naggar, the examiner reasoned that the disclosure of El-Naggar would make a device with that optimum value obvious. The examiner noted that El-Naggar suggests increasing the "efficiency" (degree of purification) of his device by increasing the contactor area while apparently keeping the "throughput" constant, that is, reducing the "hydraulic loading." The examiner then assumed that El-Naggar teaches keeping the tank volume constant while increasing the contactor area. Thus, the examiner argued that the idea of increasing tank volume to surface area to increase efficiency is taught and that working out the value for optimum efficiency is mere mechanical experimentation. The board accepted the examiner's reasoning.

#### OPINION

In determining whether the invention as a whole would have been obvious under 35 USC 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question (the ratio value) but also to those properties of the subject matter which are inherent in the subject [\*\*5] matter and are disclosed in the specification. *In re Davies*, 475 F.2d 667, 177 USPQ 381 (CCPA 1973). In this case, the invention as a whole is the ratio value of 0.12 and its inherent and disclosed property. That property is that the described devices designed with the ratio will maximize treatment capacity regardless of the values of the other variables in the devices. Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention as a whole, and not some part of it, which must be obvious under 35 USC 103. Cf. *In re Papesch*, 50 CCPA 1276, 315 F.2d 381, 137 USPQ 43 (1963). [\*620]

The controlling question is simply whether the differences (namely the value of 0.12 and its property) between the prior art and appellant's invention as a whole are such that appellant's invention as a whole would have been obvious. The answer is no. It is impossible to recognize, from the experiment taught by El-Naggar, that "treatment capacity" is a function of "tank volume" or the tank volume-to-contactor area ratio. Recognition of this functionality is essential to the obviousness of conducting experiments to determine [\*\*6] the value of the "tank volume" ratio which will maximize treatment capacity. Such functionality can only be determined from data representing either efficiency at varying tank volume, fixed throughput, and fixed contactor area or throughput at varying tank volume, fixed efficiency, and

fixed contactor area. Each of these experiments represents treatment capacity with fixed contactor area but varying tank volume. This sort of experiment would not be suggested by the teachings of El-Naggar since he was not trying to maximize or control "treatment capacity." The experiments suggested by El-Naggar do not reveal the property which applicant has discovered, and the PTO has provided us with no other basis for the obviousness of the necessary experiments.

The PTO and the minority appear to argue that it would always be obvious for one of ordinary skill in the art to try varying every parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result. <sup>4</sup> As we have said many times, obvious to try is not the standard of 35 USC 103. *In re Tomlinson*, 53 CCPA 1421, [\*\*7] 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of "obvious to try" experiments disregards the "invention as a whole" concept of § 103, *In re Dien*, 54 CCPA 1027, 371 F.2d 886, 152 USPQ 550 (1967) and *In re Wiggins*, 55 CCPA 1356, 397 F.2d 356, 158 USPQ 199 (1968), and overemphasis on the routine nature of the data gathering required to arrive at appellant's discovery, after its existence became expected, overlooks the last sentence of § 103. *In re Saether*, 492 F.2d 849, 181 USPQ 36 (CCPA 1974).

4 The precise nature of the El-Naggar experiment and the nature of the data which would result are rendered hopelessly speculative by El-Naggar's total failure to discuss the critical matter of what is done with the volume of the tank. The PTO appears to assume, as a necessary element of its conclusion, that appellant's ratio is the inevitable result of El-Naggar experiment, and that the tank volume is fixed, apparently because El-Naggar does not suggest changing the tank as additional contactor area is supplied. Even if the same tank were used, the actual liquid volume of the tank could change significantly if 1) the tank has a level control, 2) the tank is not extremely large in comparison to the contactors and 3) the volume-to-area ratio of the contactors themselves is significant. Since these assumptions are not unreasonable, there is serious doubt as to the constant volume of the tank.

Whether one would inevitably arrive at the ratio value of 0.12 or above depends on facts which must be read into El-Naggar, (e.g., the volume of the tank) and on assumptions about the kind of motivation (e.g., the degree of "efficiency" which would be sought). All of this

involves, at least on this record, mere speculation. Assuming, as the examiner has, that the tank volume is fixed and the natural motivation is to maximize efficiency, if El-Naggar's equipment has a tank volume to contactor area ratio of less than 0.12, and the resulting efficiency is found wanting, increasing the contactor area to increase "efficiency" will lead away from the claimed ratio.

[\*\*8] In *In re Aller*, 42 CCPA 824, 220 F.2d 454, 105 USPQ 233 (1955), the court set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious. We have found exceptions to this rule in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good. *In re Waymouth*, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974); *In re Saether*, *supra*. This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception. The decision of the board is reversed.

REVERSED

MILLER, J., concurs in the result.

DISSENT BY: MALETZ

DISSENT

[\*621] MALETZ, Judge, \* dissenting, with whom RICH, Judge, joins.

\* Judge of the United States Customs Court sitting by designation pursuant to 28 USC 293(d).

With all due respect, I cannot agree with the majority's interpretation of the El-Naggar patent. El-Naggar discloses the same wastewater treatment apparatus as claimed, except for the specific volume-to-surface ratio of .12 gallons per square foot as recited in the claims. However, El-Naggar generally discloses varying the number of disks (column 3, lines 31-35), the number [\*\*9] of concentric cylinders (column 4, lines 27-30), or the length of the cylinders (column 4, lines 61-62) in his apparatus in order to optimize results. Given the basic apparatus of El-Naggar and the concept of varying the number of disks in a tank in order to optimize impurity removal, I believe that it would have been well within the capabilities of the chemical engineer of ordinary skill to determine empirically, by routine experimentation, the optimum design ratio which appellant has determined and recited in his claims. That is, El-Naggar set the way, and appellant's work was what any routineer would have accomplished in following the patent teachings.

Appellant urges that the results which he determined empirically by plotting the effect of volume-to-surface ratio on impurity removal, including the specific, optimum design ratio of .12 gallons per square foot, could not have been predicted from El-Naggar. However, obviousness under 35 USC 103 does not require absolute predictability, *In re Kronig*, 539 F.2d 1300, 190 USPQ 425 (CCPA 1976), and it is sufficient here that El-Naggar clearly led the way for the routineer to arrive at the claimed apparatus.

I am in substantial [\*\*10] agreement with the board's analysis of this case, and I would affirm the board's decision.

4 of 28 DOCUMENTS

**IN THE MATTER OF THE APPLICATION OF WILLIAM J. BOESCH and  
JOHN S. SLANEY**

Appeal No. 79-597.

**UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS**

*617 F.2d 272; 1980 CCPA LEXIS 268; 205 U.S.P.Q. (BNA) 215*

March 13, 1980, Decided

**PRIOR HISTORY:** [**\*\*1**] Serial No. 587,776.

MILLER, Judge.

**COUNSEL:** *Robert F. Dropkin and Vincent G. Gioia*  
attorneys of record for appellants.

*Joseph F. Nakamura* for the Commissioner of Patents  
and Trademarks, *John W. Dewhirst* of counsel

This is an appeal from a decision of the Patent and Trademark Office ("PTO") Board of Appeals ("board") which sustained the examiner's rejection under 35 USC 103 of appellants' claims <sup>1</sup> 1 and 8-15 in view of Lamb <sup>2</sup> and Pohlman <sup>3</sup> et al. We affirm.

**OPINION BY: MILLER**

1 Serial No. 587,776 was filed on June 17, 1975.

**OPINION**

2 U.S. patent No. 3,147,155, issued September 1, 1964.

[**\*273**] Before MARKEY, Chief Judge, RICH, BALDWIN, and MILLER, Associate Judges, and MALETZ, \* Judge.

3 U.S. patent No. 3,457,066, issued July 22, 1969.

[**\*\*2**] Invention

\* The Honorable Herbert N. Maletz of the United States Customs Court, sitting by designation.

The invention embraces nickel base alloys consisting essentially of:

Metals	Percentage Ranges
aluminum	4.0-4.7
boron	0.005-0.03
carbon	0.0-0.18
chromium	13.7-15.3
cobalt	14.2-19.0
iron	0.0-4.0
molybdenum	3.8-4.8
titanium	3.0-3.7

The remainder of the alloys comprises nickel and incidental impurities. The elements in the alloys are balanced to provide an  $N_v$  value not in excess of about 2.35 <sup>4</sup> according to the following equation:

4  $N_v$  refers to the average electron vacancy concentration per atom in the matrix of the alloy.

5 Appellants state that the overall variation in N v due to chemical uncertainty is +/- 0.025 so that in reality the N v value of about 2.35 may actually extend from 2.32 to 2.38.

$$N v = 4.66 (A\% Cr + A\% Mo) + 1.71 (A\% Co) + 0.61 (A\% Ni)^6$$

6 Appellants' specification states that A% "refers to the atomic percent of the element so described."

[\*\*3] In the case of alloys within the broad range set forth above, but not balanced to meet the required N v value, room temperature ductility deteriorates, and creep <sup>7</sup> deformation increases, after prolonged exposure at elevated temperatures.

7 Creep is the permanent deformation of a metal that occurs as a result of prolonged compression or extension at or near room temperature. The Condensed Chemical Dictionary 228 (8th ed. 1971).

Appellants state that these results are attributable to formation of a deleterious phase (known as "sigma phase") in the metal after such exposure, and that the tendency of an alloy to form sigma phase is (unexpectedly) eliminated by balancing the relative amounts of its constituent elements in accordance with

the N v equation. Where the composition of an alloy has been controlled to provide an N v value of about 2.35 or less, no sigma has been found after exposure at 1500 degree F for time periods up to 7200 hours.

Claim 1 is illustrative:

1. A nickel base alloy having [\*\*4] a composition consisting essentially of up to 0.18% carbon from about 14.2% to about 19.0% [\*274] cobalt, from about 13.7% to about 15.3% chromium, from about 3.8% to about 4.8% molybdenum, from about 3.0% to about 3.7% titanium, from about 4.0% to about 4.7% aluminum, up to about 4.0% iron, from 0.005% to about 0.03% boron and the balance essentially nickel with incidental impurities, the aforementioned elements being balanced to provide an N v value not in excess of about 2.35 according to the following equation:

$$N v = 4.66 (A\% Cr + A\% Mo) + 1.71 (A\% Co) + 0.61 (A\% Ni)$$

the alloy being characterized by its freedom from precipitation of deleterious amounts of sigma-like phase after exposure at temperatures in excess of 1500 degree F for periods of time in excess of 1000 hours.

Prior Art

Lamb discloses a process for hot working age-hardenable nickel-chromium alloys. The alloys contain:

Metals	Percent by Weight
aluminum	4.0-5.4
boron	0.003-0.1
chromium	14.0-16.0
carbon	0.01-0.2
cobalt	14.0-25.0
molybdenum	3.0-5.5
titanium	3.0-4.6
zirconium	0.01-0.2

A sample alloy is heated at 1190 degree C for 1.5 hours and cooled to 1000 degree C at about [\*\*5] 1 degree C per minute, after which it may be hot worked at 1120 degree C. When hot working is complete, the alloy

will generally require a further heat treatment to develop full creep resisting properties.

Pohlman et al. disclose nickel base alloys suitable for elevated temperature operation containing:

Metals	Percent by Weight
aluminum	4.2-4.6
boron	0.025-0.035
carbon	0.04-0.07

Metals	Percent by Weight
chromium	14.5-15.5
cobalt	14.5-15.5
molybdenum	4.5-5.5
titanium	3.3-3.7

The remainder of the alloys essentially comprises nickel and incidental impurities; possibly, also, small amounts of silicon and manganese.

Both references are silent regarding an N v value requirement, although Lamb requires "a total aluminum and titanium content from about 7.75% to about 9.5%," and Pohlman et al. "prefer about 14.5-15.5 percent by weight cobalt because that range results in the best balance at elevated temperatures between such properties as tensile and rupture strengths, oxidation resistance and the ability of the sheet material to be formed or worked."

#### The Boesch Affidavit

Seven heats of alloys (appellants' Table I below), which were within the claimed composition ranges [\*\*6] but whose N v values varied from 2.40 to 2.54 (all clearly above the upper limit of 2.35 set forth in the claims), were processed and heat treated. Appellants' Table II shows that all seven heats contained sigma phase.

TABLE I  
CHEMISTRY-WEIGHT PERCENT

Heat No.	C	Cr	Ni	Co	Fe	Mo	Ti	Al	B	N v
D1-379-1	0.01	15.3	Bal.	17.9		4.5	3.6	4.7	0.023	2.53
D1-379-2	0.04	15.3	Bal.	17.9		4.6	3.6	4.7	0.022	2.54
D1-380-1	0.06	15.3	Bal.	17.5	1.0	4.6	3.6	4.7	0.021	2.51
D1-380-2	0.06	15.1	Bal.	17.4	3.5	4.5	3.5	4.6	0.020	2.40
D1-382	0.06	15.3	Bal.	18.5		4.3	3.5	4.4	0.019	2.47
D1-383	0.06	15.2	Bal.	17.7		4.3	3.6	4.4	0.020	2.43
D1-386	0.06	15.3	Bal.	18.1		4.7	3.4	4.6	0.021	2.49

TABLE II

Heat No.	Approximate w/o Sigma
D1-379-1	1.4
D1-379-2	0.9
D1-380-1	0.4
D1-380-2	0.05
D1-382	0.05
D1-383	0.3
D1-386	0.3

[\*275] The affidavit states that "any amount of sigma phase is deleterious and undesirable because of the susceptibility to embrittlement failure following exposure to high temperature."

The Board

The board agreed with the examiner [\*\*7] that the claimed alloys were prima facie obvious from the prior art, noting that there was no substantial disagreement that both Pohlman et al. and Lamb disclose alloys having compositional limits overlapping those of the claimed

alloys. Although disagreeing with the examiner's contention that there was no evidence to support the statement in the Boesch affidavit that "any amount of sigma phase is deleterious and undesirable," it agreed with the examiner that the Boesch affidavit was insufficient to overcome the prima facie case of obviousness because there was no evidence showing:

(1) the precise amounts of sigma-like phase present in compositions containing Appellants' claimed components balanced to provide  $N_v$  values just inside versus just outside Appellants' claimed "about 2.35"  $N_v$  limits; and (2) direct comparisons of sufficient mechanical properties of those compositions within and without the claimed limit, to demonstrate the alleged critical correlation of  $N_v$  limit with sigma phase content.

8 The board agreed with the examiner that "there [was no evidence showing] that an alloy having an  $N_v$  number of 2.35 is free of any amount of sigma phase, or what the sigma phase content and properties are of an alloy having an  $N_v$  number of 2.36 which is close to but outside the  $N_v$  requirements."

[\*\*8] The board also said that the showing (in the specification, set forth infra) did not establish the asserted criticality in selection of the components of the alloys according to the claimed  $N_v$  formula, because the alloys failed to meet the claimed compositional and  $N_v$  value requirements.

#### OPINION

##### The Prima Facie Case

Each of the ranges of constituents in appellants' claimed alloys overlaps ranges disclosed by Pohlman et al. and Lamb. Appellants, citing *In re Waymouth*, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974), argue that neither of the cited prior art references recognizes the problem solved by them and, therefore, cannot render the claims obvious. Upon examination of the prior art references, we do not agree. Appellants admitted in their specification that:

It has been postulated according to Pauling's theory that the criterion for the formation of sigma phase is based upon the number of electron vacancies ( $N_v$ ) in the bonding orbitals of the elements involved. Based thereon, other investigators have derived an empirical equation which includes the elements chromium, molybdenum, manganese, iron, cobalt and nickel. It is to be noted, however, that the nickel base alloys [\*\*9] to which reference is made in the present invention relate to an iron-free or low-iron composition, with only incidental amounts of an element such as manganese, and are

hardened by the aluminum and titanium rich intermetallic compound gamma prime.

U.S. patent No. 3,837,838 ('838), filed December 18, 1972, and issued September 24, 1974, was introduced into evidence by appellants and further illuminates what is meant by "Pauling's theory":

As described in an article by Linus Pauling entitled "The nature of interatomic forces in metals," published in Physical Review, 54:899, 1938, in a given metallic atom, the outer most orbitals, termed the bonding orbitals, are occupied by the bonding electrons responsible for [\*\*276] bonding the atom to its neighboring metallic atoms. At a given instant in time and on the average, the bonding orbitals are only partially occupied by the bonding electrons. Such partial occupation means that the outer orbitals are partially vacant of electrons or possess an "electron hole." The total average number of vacant orbitals in a given metallic atom is called the electron hole number of the metal ( $N_v$ ). The average electron hole number ( $N_v$ ) is the [\*\*10] resultant of adding all  $N_v$  for the participating elements in the alloy matrix. The higher the  $N_v$  of a given Co-Cr-Ni alloy the higher the chance for the precipitation of embrittling phases. The quantities of metals consumed in precipitation do not enter in calculating  $N_v$  of the alloy matrix and hence do not participate in the formation of embrittling phases. A low  $N_v$  may thus be obtained by either choosing elements of low  $N_v$  to form an alloy or by using elements that will react in the alloy and precipitate out from the alloy matrix.

Accordingly, in carrying out this invention, I have selected an alloy-base for the system which possesses a low  $N_v$ , and have strengthened the alloy base by adding elements which will have minor or no effect on raising the  $N_v$  through controlling their percentage as solutes or by eliminating their effect on  $N_v$  by formation of compounds which precipitate out.

It appears from appellants' specification that certain precipitate-hardened nickel base alloys, after being exposed to elevated temperatures for prolonged periods of time, suffered "from a marked and catastrophic decrease in room temperature ductility and a marked increase in the rate [\*\*11] of creep deformation." It was observed that other nickel base alloys having the same percentage ranges of components did not suffer such deleterious changes. The cause of the problem was believed to be the formation of an embrittling phase ("sigma"). As early as 1938, however, it was known that the higher the  $N_v$  value of a Co-Cr-Ni alloy, the higher the chance for precipitation of embrittling phases; also, that the quantities of metals consumed in precipitation did not enter into calculating the  $N_v$  value of an alloy

matrix. We are persuaded that one of ordinary skill in the art would have been guided by these principles.

In the above-quoted passage from '838, we note that lowering the N v value of a Co-Cr-Ni alloy and deletion of the metals not consumed in precipitation from the N v calculation are expressly suggested. Considering, also, that the composition requirements of the claims and the cited references overlap, we agree with the Solicitor that the prior art would have suggested "the kind of experimentation necessary to achieve the claimed composition, including the proportional balancing described by appellants' N v equation." This accords with the rule that discovery **[\*\*12]** of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977); *In re Aller*, 42 CCPA 824, 220 F.2d 454, 105 USPQ 233 (1955). Accordingly, we conclude that a prima facie case of obviousness has been established.

#### Unexpected Results

It is well settled that a prima facie case of obviousness may be rebutted "where the results of optimizing a variable, which was known to be result effective, [are] unexpectedly good." *In re Antonie*, supra, 559 F.2d at 620, 195 USPQ at 8-9, and cases cited therein. It is also well settled that proof of unexpected properties may be in the form of direct or indirect comparative testing of the claimed compounds (here, alloys) and the closest prior art. *In re Payne*, 606 F.2d 303, 316, 203 USPQ 245, 256, (CCPA 1979), and cases cited therein.

#### A. Creep Tests

Table V, set forth in appellants' specification and shown below, compares four examples of the claimed alloys with one example **[\*277]** (6-3211) of a prior art alloy and is intended to show that the measured creep of the claimed alloys is unexpectedly less than that of the prior art.

TABLE **[\*\*13]** V

Creep Tests at 1500 degree F and 37,000 psi

Alloy No.	Sample Removed After (Hours)	Measured Creep (inches per inch)
2-1422	1567.8	.0008
2-1423	1500.4	0.004
2-1425	1504.5	0.010
2-1426	1500.4	0.004
6-3211	1505.1	0.034

The measured creep of 6-3211--an alloy, appellants note, having "chemistries" within those of the references--is in excess of three to eight times greater than the creep of the claimed alloys.

The composition and N v values of the alloy heats in Table V are as follows:

Element, Weight %

Alloy No.	C	Al	Ti	Mo	Cr	Co	B	Ni	N v Value
2-1422	0.07	4.20	3.23	4.70	14.7	18.0	0.030	bal.	2.32
2-1423	0.06	4.37	3.45	4.45	14.6	17.6	0.028	bal.	2.36
2-1425	0.06	3.91	2.98	4.40	14.8	17.5	0.028	bal.	2.21
2-1426	0.05	4.20	3.19	4.50	14.5	17.5	0.030	bal.	2.27
6-3211	0.06	4.43	3.54	4.95	15.2	18.8	0.030	bal.	2.51

Although it is apparent that the molybdenum content of 6-3211 exceeds the maximum content of the claimed

alloys by 0.15%, it is clearly within the ranges of the Pohlman et al. and Lamb alloys.

However, we are not [\*\*14] persuaded that the Table V data are commensurate in scope with appellants' claims. *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230, (CCPA 1978).<sup>9</sup> Appellants claim broad ranges of elements, but the weight percent of elements in the four examples of the claimed alloys vary by relatively minor amounts. For example, the entire claimed range of carbon is .18 percent, but the tested range is only .02 (.07 minus .05); the claimed cobalt range is 4.8, but the test range is only 1.3. There is no evidence showing whether other alloys encompassed by appellants' broad claims and having elements varying by relatively major amounts also exhibit a low creep rate.

9 It is unnecessary to decide whether 6-3211 is the "best prior art." See *In re Malagari*, 499 F.2d 1297, 1302-03, 182 USPQ 549, 552-53 (CCPA 1974).

#### B. Ductility Test

Appellants' Table VI, set forth in their specification, compares the room temperature ductility of one heat of the claimed alloy (2-1426) and one heat of an alloy (6-3266) which appellants [\*\*15] state has "chemistries" within those of the references.

TABLE VI  
Room Temperature Tensile Tests

Alloy No.	Condition	U.T.S. psi	0.2% Offset Y.S. (psi)
2-1426	As-heat-treated	204,000	140,000
2-1426	As-heat-treated + exposed 5000 hrs. at 1500 degree F	157,000	100,000
6-3266	As-heat-treated	194,500	136,800
6-3266	As-heat-treated + exposed 5000 hrs. at 1500 degree F	150,500	117,500

Alloy No.	Elong. (%)	R.A. (%)	N v Value
2-1426	16.9	15.0	2.27
2-1426	16.1	14.1	2.27
6-3266	14.0	13.7	2.52
6-3266	5.0	5.5	2.52

[\*278] The marked decrease in room temperature ductility (Elong.) after prolonged elevated temperature exposure of the prior art alloy (6-3266), compared to the claimed alloy's (2-1426) essentially unchanged ductility, is contended to show an unexpected result, as was the improvement in measured creep discussed earlier. However, for the same reason that the measured creep test data of Table V are not persuasive of unexpected results, we do not regard the tensile test data of Table VI, comparing only one heat of a claimed alloy, sufficient to rebut the prima [\*\*16] facie case of obviousness of the claimed invention.

#### C. Absence of Sigma Phase

Throughout prosecution appellants have maintained that the claims define "a nickel base alloy which can be manufactured in a consistent way to remain free from a tendency to form plate-like sigma phase." The "essential concept of the present invention [is] to maintain the average number of electron vacancies at a value not exceeding about 2.35." Whereas the Pauling theory teaches that a low N v value means reduced chances for sigma phase, appellants allege that alloys meeting their



composition and N v value requirements are free from sigma phase.

As related earlier, the Boesch affidavit shows that sigma phase is present in seven alloy examples, all of which meet the composition requirements but exceed the N v value requirement of the claimed alloys. However, the affidavit contains no examples of claimed alloys showing the absence, or presence, of sigma. The remainder of the record reveals only a single example of the claimed alloy, which shows the absence of sigma.<sup>10</sup> Appellants' specification includes a photomicrograph of Table V alloy heat 2-1422, which clearly shows that absence of sigma; [\*\*17] also, a photomicrograph of Table V alloy heat 6-3211, which shows the presence of sigma. We note again that the prior art teaches that reduction of the N v value reduces the chances of sigma phase in the alloy. Here appellants tested only one example of a low N v value alloy and found no sigma-- a result consistent with both the prior art teaching and appellants' allegation that their claimed alloys are "totally free from sigma phase." " Under such circumstances, test results involving a single alloy within the broad range claimed are not sufficient to support appellants' allegation of what would, from the prior art, be unexpected."<sup>12</sup>

10 Thus, appellants have again failed to show test data commensurate in scope with the broad claims.

11 We agree with the board that the six United States patents ((1) No. 4,093,474, issued June 6, 1978; (2) No. 4,083,734, issued April 11, 1978; (3) No. 3,930,904, issued January 6, 1976; (4) No. 3,837,838, issued September 24, 1974; (5) No. 3,816,110, issued June 11, 1974; and (6) No. 3,767,385, issued October 23, 1973) introduced into the record by appellants "do support the assertion in the Boesch affidavit that 'any amount of sigma phase' is undesirable." Therefore, we have limited our analysis to the issue of the existence of sigma phase and have not extended it to include the effect of varying amounts of sigma phase.

12 [\*\*18] Where it is alleged that a certain technique for flipping coins would always produce "heads," one would hardly be persuaded by a single toss of a coin which resulted in a showing of "heads."

In view of the foregoing we hold that appellants have failed to rebut the prima facie case of obviousness.

The decision of the board is affirmed.

AFFIRMED

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

*Ex parte* GUY A. BUZZONI

Appeal 2007-3725  
Application 10/183,478  
Technology Center 3600

Decided: January 30, 2008

Before TERRY J. OWENS, JENNIFER D. BAHR, and ANTON W.  
FETTING *Administrative Patent Judges.*

OWENS, *Administrative Patent Judge.*

DECISION ON APPEAL

The Appellant appeals from a rejection of claims 1, 5-11, 15, 16, 20, 21, 26-30, 32-36, 38-42 and 44-46, which are all of the pending claims.

THE INVENTION

The Appellant claims an anchorless wheel bumper block and a wheeled parking system including that block. Claim 1 is illustrative:

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1. An anchorless wheel bumper block for use as a stop in a parking facility, the block comprising:

a base having a bottom surface, wherein the bottom surface rests on a ground surface and the block is in contact with and unattached to the ground surface in an in-use position, the bottom surface being disposed in a first plane and having a length and a width;

a top having an upper surface, the upper surface being disposed in a second plane generally parallel to the first plane and having a length substantially equal to the length of the bottom surface and a width substantially equal to the width of the bottom surface, wherein a distance between the bottom and upper surfaces defines a height of the block, the length of the bottom surface is substantially greater than the height of the block, the bottom surface has a surface area substantially equal to a surface area of the upper surface, and the upper surface is adapted to engage the bottom surface of another block such that a plurality of blocks in a non-use position may be stably stacked together to form a stack that may be moved for storage, the stack comprising single blocks stacked one on top of another;

a side extending around a perimeter of the block and between the bottom and upper surfaces, wherein the block remains substantially in the in-use position when a wheel of a wheel unit contacts the block; and

at least two channels disposed in the base, the channels having a size and spacing adapted to receive blades of a forklift to enable the bumper block to be lifted and moved.

#### THE REFERENCES

Yodock  
Angley

US 5,882,140  
US 5,902,068

Mar. 16, 1999  
May 11, 1999

### THE REJECTIONS

The claims stand rejected as follows: claims 1, 5-7, 16, 27-29, 34-36, 38-42, 44 and 45 under 35 U.S.C. § 102(b) as anticipated by Angley; claims 8, 9, 15, 20, 21, 26 and 46 under 35 U.S.C. § 103 as unpatentable over Angley; claims 10 and 11 under 35 U.S.C. § 103 as unpatentable over Angley in view of Yodock; and claims 30, 32 and 33 under 35 U.S.C. § 103 as unpatentable over Angley in view of the Appellant's prior art figures 17-19.

### OPINION

The rejections are affirmed as to claims 1, 5-7, 10, 11, 16, 26-29, 34-36, 38-42 and 44-46, and reversed as to claims 8, 9, 15, 20, 21, 30, 32 and 33.

Rejection of claims 1, 5-7, 16,  
27-29, 34-36, 38-42, 44 and 45

The Appellant does not separately argue any of the claims rejected under 35 U.S.C. § 102(b) (Br. 8-9).<sup>1</sup> We therefore limit our discussion of that rejection to one claim, i.e., claim 1. Claims 5-7, 16, 27-29, 34-36,

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<sup>1</sup> Claim 41, which depends from claim 1, requires that "the width of the bottom surface is substantially greater than the height of the block." The Appellant includes claim 41 in the argument that the Examiner has not shown that the limitations in some of the dependent claims are result effective variables (Br. 9-10; Reply Br. 4). The claim requirement in claim 41, however, is disclosed by Angley, i.e., Angley's 4 foot width is substantially greater than the first disclosed height (9 inches) (col. 8, ll. 9-14). Therefore, that claim is properly rejected under 35 U.S.C. § 102(b) (to which the Appellant's argument is irrelevant).

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38-42, 44 and 45 stand or fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(vii) (2007).

Angley discloses a cellular concrete arresting block (70) for arresting travel of an aircraft overrunning the end of a runway, or for stopping trucks or other vehicles (col. 7, ll. 49-55). Block 70 is 8 feet long, 4 feet deep and 9 to 30 inches high, has a continuous compressive gradient strength of 40-140 psi over at least 60% of its thickness, and has two transverse slots (78, 80) sized and spaced such that it can be lifted, moved and transported by a forklift (col. 8, ll. 9-19, 42-49, 50-63).

The Appellant argues that one of ordinary skill in the art would recognize that Angley's block is not a wheel bumper block because it is intended to be compressed by the wheels of an airplane to produce drag, whereas a wheel bumper block is a block which a wheel would bump off of rather than roll over (Br. 8; Reply Br. 1-2). The Appellant further argues that Angley's block 70 is adhered or bonded to the runway safety area using asphalt, cement grout, or other suitable adhesive material (col. 7, ll. 20-23; col. 11, ll. 58-60; col. 13, ll. 12-15) and, therefore, is not unattached to the ground surface in an in-use position as required by the Appellant's claim 1 (Br. 8-9; Reply Br. 2-3).

The Appellant's claim 1 is limited to a wheel bumper block itself. The claim does not require a wheel bumper block in an unattached, in-use position on the ground with a wheel of any particular type of wheeled unit contacting it. All the claim requires regarding the function as a wheel bumper block is that the block is unattached to the ground in an in-use

position, at least before being attached to the ground, and that while in that unattached position it can function as a wheel bumper block when contacted by a wheel of any type of wheeled unit. The Appellant's Specification does not define "wheel bumper block" as being limited to a bumper block for a wheel of any particular type of wheeled unit. Hence, claim 1 encompasses a wheel bumper block in a parking lot for stopping a shopping cart in a shopping cart return area, or for bumping against a bicycle tire at a bicycle parking rack, provided that the block is stackable with other blocks and has forklift channels. Angley's block 70 has forklift channels (col. 8, ll. 42-49), and the block's rectangular shape (fig. 2) renders it stackable with other blocks. Also, the block's size (8 ft x 4 ft x 9-30 inches; col. 8, ll. 9-15) and density (12-22 lb/ft<sup>3</sup>; col. 4, ll. 17-19) render it capable, in an unattached in-use position, such as when it is "placed at the site" prior to being adhered or prior to the adhesive setting (col. 7, ll. 20-23), of stopping a lightweight wheeled unit such as a shopping cart or a bicycle.

Hence, we are not convinced of reversible error in the rejection of claim 1.

#### Rejection of claim 46

Claim 46, which depends from independent claim 16 grouped above with claim 1, requires that "the anchorless wheel bumper block has a plurality of anchorless wheel bumper blocks stacked thereon in the non-use position." The Appellant does not separately argue claim 46 (Br. 9-11; Reply Br. 4-5). Claim 46, therefore, falls with claim 16.

Rejection of claims 10 and 11

Although an additional reference (Yodock) is applied in the rejection of claims 10 and 11, the Appellant does not separately argue those claims but, rather, relies upon the arguments set forth with respect to claim 1 from which those claims depend (Br. 9). Those arguments are not persuasive for the reasons given above regarding the rejection of claim 1.

Rejection of claims 8, 9, 15, 20, 21 and 26

Claim 8, which depends from claim 1, and claim 20, which depends from claim 16, require that the length of the block's bottom surface is approximately 15 ft, the width of the block's bottom surface is approximately 4 ft, and the height of the block is approximately 7 in. Claim 9, which depends from claim 1, and claim 21, which depends from claim 16, require that the block weighs approximately 5,250 lb. Claim 15, which depends from claim 1, requires a ratio of the block's bottom surface length to the block's height of approximately 25:1.

The Examiner argues that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the block of Angley et al. to have included the claimed weight, length, width, and height or any other appropriate amounts as best determined by routine experimentation, to provide appropriate structural integrity since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Bosch*, 617 F.2d 272, (CCPA 1980)" (Ans. 5-6). Even if one of ordinary skill in the art would have optimized as proposed by the Examiner, the optimum obtained would

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be the optimum for the disclosed vehicle arresting unit used as disclosed by Angley. The Examiner has not established that the optimum for a wheel bumper block would be the same as the optimum for Angley's vehicle arresting unit.

The Examiner argues that "Angley et al. state in col. 3 lines 1-5 that the geometry of the block is dependent upon properties of the material and on the application in which the block is used. Examiner maintains that the Angley et al. [sic] clearly set forth art-recognized result effective variables" (Ans. 9). Angley states, at column 3, lines 1-7: "The amount of material, and the geometry in which it is formed to provide an effective arresting bed for vehicles of a predetermined size, weight, and speed, is directly dependent upon the physical properties of the material and, in particular, the amount of drag which will be applied to the vehicle as it moves through the bed crushing or otherwise deforming the material." Thus, Angley's variables to be optimized are those of an arresting bed that is to be crushed or deformed by a vehicle. The Examiner has not established that an optimum obtained for the arresting bed would be an optimum for a wheel bumper block.

The Examiner, therefore, has not established a prima facie case of obviousness of the invention claimed in the Appellant's claims 8, 9, 15, 20 and 21.

Claim 26, which depends from claim 1, requires that "the ratio of the width of the bottom surface to the height is at least 5 to 1." Angley's width:height ratios are 4 feet:9-30 inches (col. 8, ll. 9-14). The combination



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of Angley's 4 foot width with the first of the disclosed heights, i.e., 9 inches, falls within the Appellant's recited ratio of at least 5 to 1.

The Appellant has not provided an argument specifically directed toward claim 26 and, therefore, has not persuaded us of reversible error in the rejection of that claim.

#### Rejection of claims 30, 32 and 33

Claim 30, which depends from claim 1's dependent claim 5, requires that the wheel bumper block's side extending around the perimeter of the block "further comprises a beveled portion between the upper surface and each of the first and second ends and the first and second side surfaces."

Claims 32 and 33, which depend, respectively, from independent claims 28 and 29, require that "each side surface of the first and second pairs of opposing side surfaces comprises a beveled portion."

The Appellant's prior art figures 17-19 show wheel bumper blocks having beveled sides.

The Examiner argues that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the side of the block of Angley et al. to have included beveled portions, as taught by the prior art figures, in order to reduce the amount of material in the construction of the block while maintaining structural integrity of the block" (Ans. 7-8). The Examiner further argues that "it is in the knowledge generally available to one of ordinary skill in the art to reduce material in the construction of mechanical components to provide both weight and cost savings" (Ans. 9). The Examiner, however, has not established that the

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sides of the wheel bumper block in the Appellant's prior art figures 17-19 are beveled to reduce weight and material cost, or that even if beveling the sides reduces weight and cost, one of ordinary skill in the art would have desired beveled sides in Anglely's vehicle arresting block which is to be placed next to other vehicle arresting blocks to form a vehicle arresting bed.

Hence, the Examiner has not established a prima facie case of obviousness of the inventions claimed in the Appellant's claims 30, 32 and 33.

#### DECISION

The rejection of claims 1, 5-7, 16, 27-29, 34-36, 38-42, 44 and 45 under 35 U.S.C. § 102(b) as anticipated by Anglely is affirmed. The rejection of claims 8, 9, 15, 20, 21, 26 and 46 under 35 U.S.C. § 103 over Anglely is reversed as to claims 8, 9, 15, 20 and 21, and affirmed as to claims 26 and 46. The rejection of claims 10 and 11 under 35 U.S.C. § 103 over Anglely in view of Yodock is affirmed. The rejection of claims 30, 32 and 33 under 35 U.S.C. § 103 over Anglely in view of the Appellant's prior art figures 17-19 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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hh

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437 F.3d 1157, \*, 2006 U.S. App. LEXIS 2653, \*\*;  
77 U.S.P.Q.2D (BNA) 1865

LEXSEE 437 F.3D 1157, 1165

**MEDICHEM, S.A., Plaintiff-Appellee, v. ROLABO, S.L., Defendant-Appellant.**

05-1179, 05-1248

**UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT**

*437 F.3d 1157; 2006 U.S. App. LEXIS 2653; 77 U.S.P.Q.2D (BNA) 1865*

**February 3, 2006, Decided**

**SUBSEQUENT HISTORY:** Rehearing denied by, Rehearing, en banc, denied by *Medichem, S.A. v. Rolabo, S.L.*, 2006 U.S. App. LEXIS 7669 (*Fed. Cir.*, Mar. 15, 2006)

**PRIOR HISTORY:** [\*1] Appealed from: United States District Court for the Southern District of New York. Judge Jed S. Rakoff.  
*Medichem, S.A. v. Rolabo, S.L.*, 2004 U.S. Dist. LEXIS 23697 (*S.D.N.Y.*, Nov. 19, 2004)

**DISPOSITION:** AFFIRMED-IN-PART,  
REVERSED-IN-PART.

**COUNSEL:** John G. Taylor, Frommer Lawrence & Haug LLP, of New York, New York, argued for plaintiff-appellee. With him on the brief were Barry S. White and James K. Stronski.

Thomas P. Heneghan, Michael Best & Friedrich LLP, of Madison, Wisconsin, argued for defendant-appellant. With him on the brief were Jeffrey S. Ward and Charlene L. Yager.

**JUDGES:** Before SCHALL, GAJARSA, DYK, Circuit Judges.

**OPINION BY:** GAJARSA

## **OPINION**

[\*1160] GAJARSA, Circuit Judge.

This is the second round of a protracted litigation to establish priority of invention between Stampa et al.'s *U.S. Patent No. 6,084,100* ("the '100 patent'"), assigned to Medichem, S.A. ("Medichem"), and Jackson's *U.S. Patent No. 6,093,827* ("the '827 patent'"), assigned to Rolabo, S.L. ("Rolabo"). In the first round appealed to this court, we remanded to the district court, requiring it to establish an interference-in-fact under 35 U.S.C. § 291 before determining priority. *Medichem, S.A. v. Rolabo,*

*S.L.*, 353 F.3d 928 (*Fed. Cir.* 2003) ("Medichem II"). Rolabo now appeals [\*2] from the judgment on remand, in which the United States District Court for the Southern District of New York found the existence of an interference-in-fact and awarded priority of invention to Medichem. See *Medichem, S.A. v. Rolabo, S.L.*, *Memorandum Order*, 2004 U.S. Dist. LEXIS 23697, No. 01 Civ. 3087, 2004 WL 2674632 (*S.D.N.Y.* Nov. 22, 2004) ("Medichem III"). For the reasons discussed below, we affirm the judgment of the district court on the proper establishment of the interfering subject matter and on the finding of the existence of an interference-in-fact. We reverse, however, the district court's award of priority to Medichem, based on the insufficiency of the evidence that Medichem introduced at trial to corroborate the testimony of its inventors regarding reduction to practice of the invention.

## **BACKGROUND**

### **A. The Patents**

Medichem and Rolabo are both pharmaceutical manufacturers based in Barcelona, Spain. Rolabo's '827 patent and Medichem's '100 patent both claim a process for making loratadine from two precursor chemicals via a chemical reaction known as the McMurry reaction. Loratadine is the active ingredient in the allergy medication Claritin (R). McMurry reactions involve the [\*3] coupling of two starting materials in the presence of low-valent titanium. In general, McMurry reactions can lead to two types of products, diols and alkenes; loratadine, the desired end product of this reaction, is an alkene. McMurry reactions can be optimized for alkene production by adjusting various reaction parameters, such as the temperature and length of the reaction in this case, and also by adding additional reactants. The only significant difference between the processes claimed by Medichem<sup>1</sup> and Rolabo<sup>2</sup> is that Medichem's [\*1161] process requires the reaction to be carried out in the presence of a type of chemical known as a tertiary amine.<sup>3</sup> In contrast, the Rolabo process permits by not excluding, but does not require, the presence of a tertiary

amine. Conceptually, therefore, the Medichem invention, which requires a tertiary amine, is a species within the genus of the Rolabo invention.

1 Claims 1 and 2 of Medichem's '100 patent read:

1. A process for the preparation of loratadine consisting of reacting, in an organic solvent and in the presence of a tertiary amine, 8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-one, of formula VII with a low-valent titanium species. (emphasis added).

2. The process of claim 1, wherein the low-valent titanium species are generated by reduction of titanium tetrachloride with zinc dust.

[\*\*4]

2 Claims 1 and 17 of Rolabo's '827 patent read:

1. A process for preparing 5,6-dihydro-11H-dibenzo[a,d]cyclohept-11-enes comprising reacting a dibenzosuberone or an aza derivative thereof with an aliphatic ketone in the presence of low valent titanium wherein said low valent titanium is generated by zinc.

17. A process as claimed in claim 1 for preparing Loratadine.

3 A tertiary amine is a compound in which nitrogen is bonded three times to carbon. A commonly used tertiary amine is pyridine.

#### B. Proceedings to Date

Medichem brought an action under 35 U.S.C. § 291, alleging an interference-in-fact between the '100 and '827 patents, claiming priority of invention, and seeking invalidation of Rolabo's patent under 35 U.S.C. § 102(g). Transcript of Verdict at 653-67, *Medichem, S.A. v. Rolabo, S.L.*, No. 01 Civ. 03087, 2002 U.S. Dist. LEXIS 27086 (S.D.N.Y. May 8, 2002) ("Medichem I"). Because

Rolabo was the party with the earlier effective filing date, Medichem sought to establish priority by proving an actual reduction to practice that was even earlier. After a bench trial, the district court found that there was no interference-in-fact between the claimed inventions, but it nonetheless awarded priority to Medichem. *Id.*

4 Rolabo's effective filing date is February 26, 1997 and Medichem's is May 30, 1997.

On appeal, this court vacated the priority holding, opining that because the existence of an interference-in-fact is a jurisdictional requirement under 35 U.S.C. § 291, it was therefore a precondition to the district court's consideration of the priority issue. *Medichem II*, 353 F.3d at 935-36. We explained that the first step in an interference analysis is for the court to determine whether an interference exists under 35 U.S.C. § 291 by asking whether the "patents. . . have the same or substantially the same subject matter in similar form as that required by the PTO pursuant to 35 U.S.C. § 135." *Id.* at 934 (internal quotations omitted). In order to make this determination, we use the "two-way" test which states that two patents interfere only if (1) invention *A* either anticipates or renders obvious invention *B*, where Party *A*'s claimed invention is presumed to be prior art vis-a-vis Party *B* and (2) vice versa. *Id.* (citing *Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash.*, 334 F.3d 1264, 1268 (Fed. Cir. 2003)).

In *Medichem II*, we held that Medichem's claims to the "species" would clearly anticipate Rolabo's genus claim if the Medichem patent were assumed to be prior art. *Id.* at 934-35. Thus, we held that the first prong of the two-way test was clearly satisfied. *Id.* at 935. However, we remanded to the district court for a determination of whether the second prong was also satisfied—namely, whether Rolabo's genus claim, if prior art, would either anticipate or render obvious Medichem's species claim. *Id.* at 935. We explained that "as the '827 patent contains genus claims and the '100 patent contains species claims, an arrangement that assumes that the '827 patent is prior art does not necessarily anticipate or make obvious the narrower claims of the '100 patent." *Id.*

On remand, the district court held that "assuming arguendo [pursuant to the two-way test] the priority of the '827 patent, claims 1 and 17 of the '827 patent clearly anticipate and render obvious the adding of a tertiary amine, as in the '100 patent." *Medichem III*, 2004 U.S. Dist. LEXIS 23697, 2004 WL 2674632 at \*7. Although the court went on to explain its holding on obviousness grounds, it was silent about the reasons underlying its apparent determination that Rolabo's genus claims would also anticipate Medichem's species

claim. Instead, it improperly recharacterized our remand instructions as "reducing to the question of whether it would be 'obvious' to add tertiary amine to a McMurry reaction to make loratadine." <sup>5</sup> *Id.*(emphasis added).

5 In so doing, the court appears not to have separately considered the question of whether the '827 *patent*, if taken as prior art, would anticipate the '100 *patent*.

The court then correctly stated that:

Determining obviousness requires consideration of two factors: 1) whether the prior art would have suggested to one of ordinary skill in the art that he should carry out the claimed process; and 2) whether the prior art would have also revealed that in carrying out the process, one of ordinary skill would have a reasonable expectation of success.

*Id.* The district court proceeded to articulate [**\*\*8**] factual bases for its obviousness holding, which included (1) an article that pointed to the use of amines to improve yields in coupling reactions, (2) testimony by Rolabo's expert about additional such prior art, and (3) evidence that such prior art had actually motivated Medichem's inventor's to try adding tertiary amine to the reaction mixture. *Medichem III*, 2004 U.S. Dist. LEXIS 23697, 2004 WL 2674632 at \*7-8.

Having found the two-way test's second prong to be satisfied on both anticipation and obviousness grounds, the district court concluded that the Medichem and Rolabo patents interfered, a finding that gave it jurisdiction over the priority dispute pursuant to 35 U.S.C. § 291. It awarded priority to Medichem, after finding that the invention claimed in the '100 *patent* was reduced to practice prior to the constructive reduction to practice date of Rolabo's invention. See 2004 U.S. Dist. LEXIS 23697, [WL] at \*10-11 (referring to Medichem I and stating that the court "reinstates and reaffirms its former priority ruling").

In finding reduction to practice, the court neither explicitly discussed the legal requirement that reduction to practice be corroborated by independent evidence, [**\*\*9**] nor made a factual finding of corroboration. However, it dismissed Rolabo's argument that Medichem's inventors were not credible as a result of having fraudulently backdated documents that it had offered to show reduction to practice in 1995. The court thus affirmed its finding in Medichem I that Medichem had provided adequate proof of reduction to practice in 1996. The court did so notwithstanding its previous

observation that "the willingness of Medichem to fraudulently backdate [evidence of reduction to practice in 1995], coupled with Medichem's less than punctilious recordkeeping practices . . . does convince the Court that it cannot place the same reliance on plaintiff's testimony and documents as it might otherwise have." Transcript of Verdict at 658, Medichem I. However, the court apparently adhered to [**\*1163**] its view that Medichem's fraudulent backdating was "chiefly a belated attempt to deal with their noncompliance with [certain] regulatory requirements." *Id.* The Medichem III court therefore reaffirmed its award of priority to Medichem, and Rolabo appealed on February 9, 2005. This court has jurisdiction pursuant to 28 U.S.C. § 1295 [**\*\*10**] (a)(1).

As an aside, we wish to note that in parallel with the district court proceedings under 35 U.S.C. § 291, the Board of Patent Appeals and Interferences ("Board") has been considering essentially the same interference and priority issues pursuant to 35 U.S.C. § 135. See *Stampa v. Jackson*, 2002 Pat. App. LEXIS 191, 65 U.S.P.Q.2d 1942 (B.P.A.I. 2002) (involving an interference between Medichem's then-pending reissue application and both Rolabo's patent and a pending continuation application thereof, giving rise to Patent Interference Nos. 105,069 and 105,212). The Board held that the district court's holding in Medichem I did not bar the Board proceedings on grounds of issue preclusion. See *id.* at 1945-47.

Shortly after the district court's remand decision in Medichem III, the Board resolved the interference in favor of Rolabo, reaching a conclusion opposite to that of the district court. See *Stampa v. Jackson*, 76 U.S.P.Q.2d (BNA) 1105, Inter. Nos. 105,069 & 105,212, 2005 Pat. App. LEXIS 12, 2005 WL 596770 (B.P.A.I. January 25, 2005). Central to its decision was Medichem's failure to corroborate its account of an alleged actual reduction [**\*\*11**] to practice with evidence independent of its inventors' testimony. 76 U.S.P.Q.2d (BNA) 1105, 2005 Pat. App. LEXIS 12, [WL] at \*19-20. The Board noted that "all of the evidence regarding an experiment on May 7, 1996 which is said to have obtained loratadine via a process of the count and conducted by [non-inventor] Lola Casas and said to be recorded [in her notebook] is based on the testimony of [Medichem inventors]." 76 U.S.P.Q.2d (BNA) 1105, 2005 Pat. App. LEXIS 12, [WL] at \*15. Significantly, Medichem did not produce any testimony from Casas, a failure that the Board perceived as sufficient to permit the inference that Casas' testimony would have been adverse to Medichem. 76 U.S.P.Q.2d (BNA) 1105, 2005 Pat. App. LEXIS 12, [WL] at \*20. However, the Board declined to apply such an adverse inference on the grounds that "[Medichem's] case is so weak, we find it unnecessary to draw an inference one way or the other." <sup>6</sup> *Id.* While appellant does not argue that the Board

decision as a binding effect on this court, Board decisions nevertheless represent the views of a panel of specialists in the area of patent law. Medichem has appealed the Board's decision to this court. See *Stampa v. Jackson*, appeal docketed, Nos. 06-1004 & -1029 (Fed. Cir. Oct. 6, 2004 & Oct. 24, 2004).

6 A final judgment on the merits was issued the same day. See *Stampa v. Jackson*, 76 U.S.P.Q.2d (BNA) 1105, *Inter. Nos.* 105,069 & 105,212, 2005 *Pat. App. LEXIS* 12, 2005 *WL* 596770 (B.P.A.I. January 25, 2005). The Board later denied Medichem's request for rehearing, stating *inter alia* that "the importance of Lola Casas' testimony is manifest. She is the principal, if not the only, corroborating witness on the issue of whether an actual reduction to practice took place." See *Stampa v. Jackson*, *Inter. Nos.* 105,069 & 105,212, 2006 *Pat. App. LEXIS* 40, 2005 *WL* 1541082 (B.P.A.I. June 27, 2005).

## [\*\*12] DISCUSSION

There are three issues in this case—namely, whether the district court (1) erred in finding the existence of an interference-in-fact; (2) committed reversible error in failing to formally define a count corresponding to the interfering subject matter; and (3) erred in awarding priority of invention to Medichem based on the oral testimony of Medichem co-inventors, testimony that Rolabo claims was not corroborated by independent evidence, and thus should not have been credited in the final determination of whether reduction to practice was established before the critical date.

### [\*1164] A. Existence of an Interference-in-Fact

For the reasons explained below, we agree that under the second prong of the two-way test for obviousness, Rolabo's genus claim renders obvious the Medichem species claim. We therefore affirm the lower court's finding of an interference-in-fact without needing to review the district court's unsupported factual finding that the second prong of the two-way test was independently satisfied on anticipation grounds.

#### 1. Standard of Review

In reviewing a district court's finding of an interference-in-fact pursuant to the two-way test, this court reviews, where [\*\*13] necessary, both the subsidiary findings of anticipation and/or obviousness as they relate to the application of the test. See *Medichem II*, 353 F.3d at 932 (articulating the standard of review for findings of an interference-in-fact under 35 U.S.C. § 291). Here, because we agree with the district court's subsidiary finding of obviousness, which is sufficient to support its finding of an interference-in-fact, it is not

necessary for us to review the court's finding of anticipation.

Obviousness under 35 U.S.C. § 103 is a legal conclusion that is reviewed *de novo*; however, it is based in turn on underlying factual determinations which are reviewed for clear error. *Id.* Under the clear error standard, a reversal is permitted "only when this court is left with a 'definite and firm conviction' that the district court was in error." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004) (quoting *Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562 (Fed. Cir. 1996)).

#### 2. Obviousness

The ultimate determination of whether an invention would have been obvious under 35 U.S.C. § 103 [\*\*14] (a) is a legal conclusion based on the factual Graham findings, e.g., "(1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art." *Velandier v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)).

This court has held that if all the elements of an invention are found in a combination of prior art references:

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

*Id.*

The first requirement, the motivation to combine references, serves to prevent hindsight bias. See *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351 (Fed. Cir. 2001) ("To prevent hindsight invalidation of patent [\*\*15] claims, the law requires some 'teaching, suggestion or reason' to combine cited references.") (quoting *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573 (Fed. Cir. 1997)). In making obviousness determinations, the test is "whether the subject matter of the claimed inventions would have been obvious to one skilled in the art at the time the inventions were made, *not* what would be obvious to a judge after reading the

patents in suit and hearing the testimony." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092 (Fed. Cir. 1985). Whether such a motivation [\*1165] has been demonstrated is a question of fact. See *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348 (Fed. Cir. 2000). Evidence of a motivation to combine prior art references "may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000).

When a piece of prior art "suggests that the line of development flowing from the reference's disclosure is unlikely [\*16] to be productive of the result sought by the applicant" the piece of prior art is said to "teach away" from the claimed invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). As with other subsidiary obviousness inquiries, "what a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact." *Winner*, 202 F.3d at 1349 (internal quotations omitted). However, obviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness. Likewise, a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine. See *id.* at 1349 n.8 ("The fact that the motivating benefit comes at the expense of another benefit, however, should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another."). Where the prior art contains "apparently conflicting" teachings (i.e., where some references teach the combination and others [\*17] teach away from it) each reference must be considered "for its power to suggest solutions to an artisan of ordinary skill. . . . considering the degree to which one reference might accurately discredit another." *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991).

As stated above, an obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination. While the definition of "reasonable expectation" is somewhat vague, our case law makes clear that it does not require a certainty of success. See *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success. . . . All that is required is a reasonable expectation of success.").

However, to have a reasonable expectation of success, one must be motivated to do more than merely to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters [\*18] were critical or no direction as to which of many possible choices is likely to be successful." *Id.* at 903. Similarly, prior art fails to provide the requisite "reasonable expectation" of success where it teaches merely to pursue a "general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.*

The district court's finding of a reasonable expectation of success is a question of fact, which we review for clear error. See *Ruiz*, 357 F.3d at 1275 (explaining that the obviousness determination rests on "various factual findings that this court reviews for clear error following a bench trial"); *Brown & Williamson*, 229 F.3d at 1129 [\*1166] (reviewing the district court's finding of reasonable expectation of success under the clear error standard); see also *Velandier v. Garner*, 348 F.3d 1359, 1376 (Fed. Cir. 2003) (reviewing the Board of Patent Appeals and Interferences' finding of a reasonable expectation of success under a "substantial evidence" standard).

### 3. Analysis

Rolabo argues that the [\*19] district court erred in finding that the Medichem invention (which uses a tertiary amine) would have been obvious over the broader Rolabo invention (which does not require it). Specifically, it appears to argue both that the prior art contained no motivation to combine references so as to have encouraged one reasonably skilled in the art to have added a tertiary amine to a McMurtry reaction and that an artisan, even if motivated to add a tertiary amine to Rolabo's process, would have had no reasonable expectation of succeeding in making loratadine via a McMurtry reaction in the presence of a tertiary amine.

In support of its arguments, Rolabo cites the trial testimony of an expert witness who explained that a seminal review article in the field showed that a tertiary amine could have "a positive effect, a negative effect, and in some cases, both a positive and negative effect" on the McMurtry reaction. Rolabo goes on to cite prior art references that disclose negative effects and essentially argues that the existence of prior art references that teach away from the invention clearly negates the motivation to combine and that the district court's finding of motivation was clearly erroneous. [\*20] We disagree.

Granted, it is clear that the prior art disclosed not only potential advantages of using a tertiary amine in a



McMurry reaction but also potential disadvantages. On the one hand, some pieces of prior art taught that low concentrations of a tertiary amine could sometimes be used to improve the yield of reactions or to avoid the formation of undesirable rearranged products. On the other hand, other references reported that tertiary amines could sometimes promote the formation of undesirable diol side-products and that when they were used as the reaction solvent (i.e., when tertiary amines are present at their highest possible concentrations), they could stop the reaction completely.

We also note the ambivalence of Medichem co-inventor Dr. Onrubia toward the introduction of a tertiary amine to the reaction mixture. On the one hand, she testified that she had added a tertiary amine "because the literature said that it might be possible to use tertiary amines in the reaction, that it wouldn't interfere, that it wasn't incompatible, and it's habitual in these circumstances to try various options until you get the reaction to work." On the other hand, when asked, "Is this purely [\*\*21] hit or miss or is there some logical cause . . . for believing that tertiary amine would add something?" she responded: "Frankly, as an organic chemist I have no reason to say that there were grounds for expecting anything from the addition of tertiary amine."

As we have explained above, the fact that some teachings in the prior art conflict with others does not render the findings of the district court clearly erroneous per se. Rather, the prior art must be considered as a whole for what it teaches. We understand the prior art, viewed as a whole, to teach that the addition of a tertiary amine sometimes works to improve the yield of McMurry reactions, especially when a tertiary amine is used in relatively low concentrations. In light of this, we cannot say that the district court clearly erred in finding that the prior art would have provided the skilled artisan with a [\*\*1167] motivation to combine references so as to use pyridine in the McMurry reaction. We wish to emphasize that this is not a case where the prior art's lack of definiteness or certainty about the result of using a tertiary amine in a specific reaction system renders the inventive subject matter "obvious to [\*\*22] try" but not obvious. While we have made clear that "'obvious to try' is not the standard under § 103, . . . the meaning of this maxim is sometimes lost." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). In *O'Farrell*, we opined that:

[This] admonition . . . has been directed mainly at two kinds of error[, namely where] . . . what would have been "obvious to try" would have been . . . to vary all parameters or try each of numerous possible choices . . . where the

prior art gave . . . no direction as to which of many possible choices is likely to be successful[or] . . . to explore . . . a promising field of experimentation, where the prior art gave only general guidance . . .

*Id.* (citations omitted). In the instant case there are not numerous parameters to vary. Rather, the principal parameter is the concentration of tertiary amine that should be used, and the prior art teaches that if the tertiary amine were to have any positive effect at all, it would be when it was present at low concentrations. Likewise, this is not a case where the prior art gives merely general guidance. In contrast, the guidance is quite clear—namely, that [\*\*23] McMurry reactions of this kind can sometimes be optimized by adding low levels of a tertiary amine.

For the aforementioned reasons, we find no clear error in the district court's determination that skilled artisans in possession of the Rolabo patent and the prior art would have not only been motivated to add a tertiary amine but that they would have possessed a reasonable expectation that they would succeed in optimizing the reaction. Reviewing de novo the trial court's application of these factual findings to reach the legal conclusion of obviousness, we likewise find no error. Accordingly, we agree with the district court's determination that the addition of a tertiary amine to a McMurry reaction would have been obvious in view of the Rolabo patent and the prior art. Because this obviousness finding satisfies the second prong of the two-way test for an interference-in-fact, we affirm the district court's determination that an interference-in-fact existed.

As a final matter, we note that we find no merit in Rolabo's contention that we should exclude from the subject matter of the interference that portion of its invention that is directed to running reactions where titanium [\*\*24] is present in specific concentration ranges (claims 10 and 11 of the '827 patent). Claim 10 requires a relative titanium concentration of 1.5:1 to 4:1, and claim 11 requires a ratio of 2:1 to 3:1. The district court relied on the testimony of Medichem's expert witness, Dr. Finney, in holding that all of the various claims of the '827 patent were "essentially identical to one another and substantially the same as claim 2 of Medichem's patent." See *Medichem III*, 2004 U.S. Dist. LEXIS 23697, 2004 WL 2674632 at \*4. Rolabo argues that Finney's expert testimony was "conclusory" and therefore insufficient to establish an interference. However, it is clear from the record that Finney's testimony was far from conclusory. In fact, Finney provided a solid factual basis for his opinion, stating that

"claim 10 says that you should have between, a ratio of one and a half to 4 to 1 titanium to dibenzosuberone. Claim 11 states the range should be 2 to 1 to 3 to 1. These are both perfectly normal ranges. And in fact, the patent examples in the '827 [Rolabo's] patent specify I think about a 2.2 to 1 ratio. . . ."

[\*1168] Indeed, other evidence of record also supports the conclusion that these are normal [\*\*25] ranges. The Banerji reference discloses ratios of 2:1 and 1:1, Ishida discloses ratios of 1.5:1, 2.5:1 and 5:1, and Lenoir discloses a ratio of about 1:1.

In short, it is clear that Rolabo's claims 10 and 11 are directed to titanium ratios that are entirely within the range of the prior art, and this fact is dispositive. This court has held that "selecting a narrow range from within a somewhat broader range disclosed in a prior art reference is no less obvious than identifying a range that simply overlaps a disclosed range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Moreover, when "the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap." *Id.* We have explained that the "normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Id.* Therefore, because Rolabo's claims 10 and 11 are directed to ratios that are entirely within the prior art, the district court properly held those claims to be part of the interfering subject [\*\*26] matter pursuant to the two-way test.

#### B. Identification of Interfering Subject Matter

Having affirmed the district court's determination that an interference-in-fact exists, and that it properly includes those claims directed to specific titanium ratios, this court turns to address Rolabo's procedural argument that the district court erred when it failed to comply with the Board's practice of articulating a precise count of the interference prior to making priority determinations.

This court has not yet addressed "whether district courts handling interfering patent suits under § 291 must define this interfering subject matter in a way similar to a count." *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256, 1264 (Fed. Cir. 2002). Nevertheless, we have made clear that at least "a single description of the interfering subject matter is necessary for a determination of priority." *Id.*

That said, *SlipTrack* does not require a court to refer explicitly to the interfering subject matter as a "count," and we believe that in this case the district court was clear about the identity of the interfering subject matter, stating in its opinion "all the various claims [\*\*27] of the '827 patent are essentially identical to one another and substantially the same as claim 2 of Medichem's patent." *Medichem III*, 2004 U.S. Dist. LEXIS 23697, 2004 WL 2674632 at \*4. Moreover, to the extent that the district court may not have been clear about whether the tertiary amine limitation was part of the interfering subject matter, we can resolve this issue on appeal. See *Slip Track*, 304 F.3d at 1264-65 (holding that where "the parties . . . dispute only whether one limitation is part of the interfering subject matter, and determination of this issue is dependent upon issues of law alone, we will resolve this issue on appeal.") Accordingly, we hold that the interfering subject matter in this case does not include the limitation of the tertiary amine, and corresponds to claim 17 of Rolabo's '827 patent. See *id.* 1265 ("Since the claims of the '760 patent do not include a wallboard . . . the wallboard cannot be an element of the interfering subject matter in this case, even though it is a limitation in the claims of the '203 patent.").<sup>7</sup>

7 We note that in parallel interference proceedings, pursuant to 35 U.S.C. § 135, the Board reached a similar definition of the count. See *Stampa v. Jackson*, 2002 Pat. App. LEXIS 191, 65 U.S.P.Q.2d 1942, 1948 (B.P.A.I. 2002) (defining the count as Jackson's (Rolabo's) claim 17).

#### [\*\*28] [\*1169] C. Priority of Invention

Finally, we review the district court's award of priority of invention to Medichem. Because the Medichem '100 patent issued from an application that had a later effective filing date than did Rolabo's '827 patent application, see *supra* note 4, Medichem bears the burden of establishing priority by a preponderance of the evidence. See *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1365 (Fed. Cir. 2004) ("Under 35 U.S.C. § 291, a party that does not have the earliest effective filing date needs only to demonstrate by a preponderance of the evidence that it was the first to invent if the two patents or applications at issue were co-pending before the PTO . . ."). Medichem bears no heightened burden, because neither patent enjoys a statutory presumption of validity. See *id.* ("The presumption of validity is nonexistent and the preponderance of the evidence burden is appropriate even if both of the patents have issued by the time a section 291 interference proceeding is initiated in a district court.").

We have held that "priority of invention goes to the first party to reduce an invention to practice unless the

[\*\*29] other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice." *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). Here, because neither party relied on a date of conception, priority is properly awarded to the party that was the first to reduce its invention to practice, either actually or constructively. Rolabo relies on its date of constructive reduction to practice, namely its February 26, 1997 effective filing date. Medichem, on the other hand, alleges that it achieved an actual reduction to practice in the spring of 1996, a date which if proven would antecede Rolabo's filing date, and thereby entitle it to priority. See supra note 4 (effective filing dates).

In order to establish an actual reduction to practice, Medichem must establish three things: "(1) construction of an embodiment or performance of a process that met all the limitations of the interference count; (2) . . . determination that the invention would work for its intended purpose," *Cooper*, 154 F.3d at 1327; and (3) the existence of sufficient evidence to corroborate [\*\*30] inventor testimony regarding these events, see *id.* at 1330 ("In order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence."). The key issue on appeal is the last one, namely whether Medichem provided adequate corroboration of the inventors' testimony regarding the alleged actual reduction to practice.

For purposes of conceptual clarity, as well as clarity of language, it should be noted that no similar condition of "corroboration" is imposed on an inventor's notebook, or indeed on any documentary or physical evidence, as a condition for its serving as evidence of reduction to practice. See, e.g., *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577-78 (Fed. Cir. 1996) (explaining that "this court does not require corroboration where a party seeks to prove conception through the use of physical exhibits because the trier of fact can conclude for itself what documents show, aided by testimony as to what the exhibit would mean to one skilled in the art"); *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993) ("Only the inventor's testimony requires corroboration [\*\*1170] before it [\*\*31] can be considered."). Of course, the credibility (and therefore the corroborative value) of an inventor's notebook may vary. Nevertheless, a notebook, unlike the oral testimony of an inventor, may be weighed, for whatever it is worth, in the final determination of reduction to practice. However, in a case involving reduction to practice, an unwitnessed notebook is insufficient on its own to support a claim of reduction to practice. See *Reese v. Hurst*, 661 F.2d 1222, 1232 (CCPA 1981) ("The inventors' notebooks are accorded no more weight than the inventors' testimony in this instance, since they were not witnessed or signed

and were unseen by any witness until after this interference was declared."); *Hahn v. Wong*, 892 F.2d 1028, 1033 (Fed. Cir. 1989) (stating that "affiants' statements that by a certain date they had 'read and understood' specified pages of Stephen Hahn's laboratory notebooks did not corroborate a reduction to practice . . . because they established only that those pages existed on a certain date . . . [and] did not independently corroborate the statements made on those pages"); *Singh v. Brake*, 222 F.3d 1362, 1370 (Fed. Cir. 2000) [\*\*32] (stating that *Hahn v. Wong* did not nullify the value of laboratory notebooks in corroborating conception because "the standard of proof required to corroborate a reduction to practice [is] more stringent . . . than that required to corroborate a conception.").<sup>8</sup> Once properly admitted into evidence, documentary and physical evidence is assigned probative value and collectively weighed to determine whether reduction to practice has been achieved. This is what is meant by the maxim that documentary and physical evidence do not require "corroboration."

8 Cf. *Stern v. Trs. of Columbia Univ.*, 434 F.3d 1375, 2006 U.S. App. LEXIS 1015, No. 05-1291, slip op. at 5 (Fed. Cir. Jan. 17, 2006) ("Regardless of the contents of the notebooks, unwitnessed laboratory notebooks on their own are insufficient to support his claim [of conception, and therefore] of co-inventorship.").

#### 1. Corroboration

Credibility concerns undergird the corroboration requirement, the purpose of which is to prevent fraud. See *Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003) ("The purpose of corroboration . . . is to prevent fraud, by providing independent confirmation of the inventor's testimony.") (internal [\*\*33] quotations omitted). As such, the corroboration requirement provides an additional safeguard against courts being deceived by inventors who may be tempted to mischaracterize the events of the past through their testimony. See *Mahurkar*, 79 F.3d at 1577 ("While perhaps prophylactic in application given the unique abilities of trial court judges and juries to assess credibility, the rule provides a bright line for both district courts and the PTO to follow in addressing the difficult issues related to invention dates.").

Sufficiency of corroboration is determined by using a "rule of reason" analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony. See *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993) ("A rule of reason" analysis is applied to determine whether the inventor's prior conception testimony has been corroborated."); *Berges v. Gottstein*, 618 F.2d 771, 776 (CCPA 1980) ("In the final

analysis, each corroboration case must be decided on its own facts with a view to deciding whether the evidence as a whole is persuasive.").

The requirement of independent knowledge [\*\*34] remains key to the corroboration inquiry. See *Reese v. Hurst*, 661 F.2d 1222, 1225 (CCPA 1981) ("Adoption of the 'rule of reason' has not altered the [\*\*1171] requirement that evidence of corroboration must not depend solely on the inventor himself."). "Independent corroboration may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor." *Id.* One consequence of the independence requirement is that testimony of one co-inventor cannot be used to help corroborate the testimony of another. See, e.g., *Lacks Indus. v. McKechnie Vehicle Components USA, Inc.*, 322 F.3d 1335, 1350 (Fed. Cir. 2003) (opining that the Special Master rightly refused to accept cross-corroboration of oral testimony as being adequate).

Despite the importance of the independence requirement, however, "the law does not impose an impossible standard of 'independence' on corroborative evidence by requiring that every point of a reduction to practice be corroborated by evidence having a source totally independent of the inventor. [\*\*35] . . ." *Cooper v. Goldfarb*, 154 F.3d at 1330 (internal quotations omitted). Similarly, "it is not necessary to produce an actual over-the-shoulder observer. Rather, sufficient circumstantial evidence of an independent nature can satisfy the corroboration requirement." *Id.*

When an inventor claims a process for making a chemical compound rather than the compound itself, it is the successful reduction to practice of the process that must be corroborated, and not merely the successful production of the compound per se. Thus, spectral evidence that might be sufficient per se to corroborate a claim directed to the product will generally not be sufficient to corroborate a claim directed to the process, in the absence of some evidence to corroborate that the product was produced via that process.

## 2. Standard of Review

Whether or not corroboration exists is a question of fact, the district court's determination of which we review for clear error. This is true because "issues of conception and reduction to practice are questions of law predicated on subsidiary factual findings," *Eaton v. Evans*, 204 F.3d 1094, 1097 (Fed. Cir. 2000), and corroboration [\*\*36] is properly viewed as a subsidiary factual finding. See *Singh v. Brake*, 222 F.3d at 1368 (implying that corroboration is a question of fact by holding that "substantial evidence supports the Board's

finding that this notebook entry alone was insufficient to corroborate Singh's testimony . . .") (emphasis added).

Before reviewing the determination of the court below, we note that it is true that corroboration is fundamentally about "credibility," see *supra* Discussion, Part C.1, and that in reviewing factual findings under the clear error standard, this court "gives great deference to the district court's decisions regarding credibility of witnesses." See *Ecolchem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1378-79 (Fed. Cir. 2000) (internal quotations omitted). Indeed, such deference is appropriately accorded to assessments of witness credibility because "only the trial judge can be aware of the variations in demeanor and tone of voice that bear so heavily on the listener's understanding of and belief in what is said." *Anderson v. Bessemer City*, 470 U.S. 564, 575, 105 S. Ct. 1504, 84 L. Ed. 2d 518 (1985).

Nonetheless, such deference is often [\*\*37] of little consequence in a corroboration inquiry because the *raison d'être* of the corroboration requirement is our refusal to base priority determinations on a court's uncorroborated assessments of a testifying inventor's credibility. Even the most credible inventor testimony is a fortiori required to be corroborated by independent [\*\*1172] evidence, which may consist of documentary evidence as well as the testimony of non-inventors. To the extent that a district court's finding of corroboration rests on its assessment of the credibility of non-inventor testimony, we apply the deferential standard of review stated in *Ecolchem*. To the extent that it rests, as it does here, on the district court's assessment of documentary, as opposed to testimonial evidence, we still apply clear error review; however, clear error is less difficult to establish.

## 3. Analysis

The parties in this case dispute whether or not there was adequate corroboration of the inventors' testimony that Medichem had actually reduced to practice the process of the claimed invention before Rolabo's effective filing date. Medichem put forward two principal types of corroborating evidence: documentary evidence generated [\*\*38] by inventors and that generated by non-inventors.<sup>9</sup>

<sup>9</sup> This patent bore a number of co-inventors, many of whom testified at trial. As we have noted above, the testimony of one inventor cannot be corroborated by the testimony of co-inventors.

In the first category, it produced a documented request for the analysis of a sample, purported to have been produced via the claimed synthetic route, which was sent by one co-inventor to another. Also in this category were the NMR spectral data obtained by the co-

inventor pursuant to that request. These spectra were consistent with loratadine, and the accuracy of that chemical identification is not being challenged. Finally, this category includes the original laboratory notebook of co-inventor Dr. Rodriguez. In the second category, documentary evidence by non-inventors, there is the original laboratory notebook of former Medichem employee, and non-inventor, Lola Casas.

This court now turns to consider the corroborative value of the three principal pieces of potentially corroborative evidence: the NMR spectra, the notebooks of Medichem's inventors, and the notebook of non-inventor Casas. We note at the outset that the [\*\*39] problem with the dated NMR data is that at most they corroborate that the inventors were in possession of the chemical loratadine as of that date; they do not, in themselves, adequately corroborate the claimed process, as they do not establish whether the sample that was analyzed was actually produced by that process. If this case dealt with a claim to a composition of matter, rather than to a process, the NMR evidence might very well take on a different relevance in this regard. As far as the corroborative value of the inventors' notebooks is concerned, they were not witnessed, and they do not provide an "independent" source of authority on the issue of reduction to practice. Hence, they have minimum corroborative value.

It is clear to this court, therefore, that Medichem's claim of corroboration stands or falls with the modicum of additional corroborative value that can properly be assigned to non-inventor Casas' notebook.<sup>10</sup> However, Casas did not testify [\*\*1173] regarding the notebook or the genuineness of its contents. In addition, although Casas' notebook was dated, it was neither signed nor witnessed, and inventor Rodriguez testified that she and Casas had made entries in each [\*\*40] others' notebooks. Rodriguez characterized these occasions as not out of the ordinary. As a result, the district court was clearly reliant on the inventor to help to identify the author of specific entries made in Casas' notebook, because in a reduction to practice inquiry, only those passages of the unsigned, unwitnessed notebooks authored by non-inventor Casas could possess significant corroborative value. In addition, without testimony from Casas, the court lacked any non-inventor testimony regarding the genuineness of the notebook's contents.

10 When an inventor attempts to offer into evidence the notebook of a non-inventor as evidence of corroboration, evidentiary issues might be implicated. For example, the notebook is likely to be hearsay, and if so, there may be an issue as to whether or not it falls within an

exception to the hearsay rule, such as the business record exception. Indeed, in *Chen v. Bouchard*, this court affirmed the decision of the Board of Patent Appeals and Interferences to exclude as inadmissible hearsay a non-inventor's notebooks, which had been offered to corroborate reduction to practice where, as in the instant case, the non-inventor did not testify. 347 F.3d 1299, 1308 (Fed. Cir. 2003).

[\*\*41] We also note that Medichem admitted fraudulently backdating certain documents relating to a purported 1995 reduction to practice. Even though the backdating of the 1995 documents was unrelated to the critical pages in Casas' notebook, which purport to establish a reduction to practice in 1996, the district court found that the credibility of the Medichem inventors was accordingly diminished.

Where a laboratory notebook authored by a non-inventor is offered into evidence pursuant to authentication by an inventor, where the author of the notebook has not testified at trial or otherwise attested to its authenticity, and where the notebook has not been signed or witnessed and has not been maintained in reasonable accordance with good laboratory practices sufficient to reasonably ensure its genuineness under the circumstances, then the corroborative value of the notebook is minimal. Given the facts of this case, Casas' notebook should therefore not be accorded much corroborative value. In view of the minimal corroborative value of the inventors' notebooks and the limited value of the NMR spectrum, we conclude that the evidence, evaluated as a whole under the rule of reason, is [\*\*42] insufficient as a matter of law to corroborate Medichem's reduction to practice.

The district court did not specifically address corroboration in its obviousness inquiry, a fact that might, in some circumstances, hamper our ability to conduct clear error review. Here, however, the facts of the case admit of only one conclusion as a matter of law, and we therefore decide the case without remanding to the district court for an explanation of why it implicitly found corroboration to be present. We hold that corroboration is absent and that the district court therefore erred in reaching its legal conclusion that Medichem had reduced its invention to practice in the spring of 1996. Accordingly, we reverse the district court's award of priority to Medichem.

AFFIRMED-IN-PART, REVERSED-IN-PART

No costs.

LEXSEE 927 F.2D 588



Positive  
As of: Sep 21, 2007

IN RE D. RAYMOND YOUNG and JOHN C. WRIDE

No. 90-1368

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

*927 F.2d 588; 1991 U.S. App. LEXIS 3386; 18 U.S.P.Q.2D (BNA) 1089*

March 5, 1991, Decided

**PRIOR HISTORY:** **[\*\*1]** Appealed from U.S. Patent & Trademark Office Board of Patent Appeals & Interferences.

**DISPOSITION:** Affirmed.

**COUNSEL:** Richard F. Phillips, Jr., Exxon Company, U.S.A., of Houston, Texas, argued for Appellants.

Lee E. Barrett, Associate Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for Appellee. With him on the brief was Fred E. McKelvey, Solicitor.

**JUDGES:** Newman, Lourie, and Rader, Circuit Judges.

**OPINION BY:** RADER

## OPINION

**[\*589]** RADER, Circuit Judge.

Raymond Young and his co-inventor John Wride (collectively Young) appeal from the October 31, 1989 and April 18, 1990 decisions of the Board of Patent Appeals and Interferences (Board). These decisions affirmed the final rejection of all claims in their application. The Board held Young's claimed invention obvious under 35 U.S.C. § 103. This court affirms.

## BACKGROUND

Young's application discloses a method and apparatus for generating an acoustic pulse in water. Acoustic pulse technology facilitates offshore seismic exploration. The acoustic pulse generates a large gas bubble in the ocean above geological formations on the ocean floor.

The rapid expansion and collapse of the gas bubble create a shock wave in the water. The shock wave propagates through the water into the **[\*\*2]** formations below the ocean bed. As the shock wave passes downward through these formations, each interface between adjoining earth strata reflects a portion of the shock wave. These reflections move upward through the ocean. Hydrophones at the ocean's surface can monitor these reflections. From these monitored reflections, geologists can generate a "seismic section" map which shows the configuration of strata in the ocean bed.

Today's most common sources of seismic shock waves are air guns. These air guns feature a chamber for storing and releasing on command highly compressed air. A high-pressure hose charges the gun with compressed air for rapid firing during a seismic survey.

Acoustic pulse technology suffers from problems with bubble oscillation. Upon release of the compressed air, the bubble undergoes a rapid initial expansion and collapse. Several more expansions and collapses follow the initial collapse, but with diminishing amplitude. Each of these expansion-collapse events creates an additional shock wave. The geological strata reflect each of these additional shock waves. The multiple reflections, in turn, blur the resolution of the seismic section. Most blurring comes from **[\*\*3]** the first oscillation after the initial bubble collapse.

**[\*590]** Acoustic pulse technology uses a "primary-to-bubble ratio" to measure susceptibility to oscillation. This ratio compares the shock wave intensity of the initial expansion-collapse to the intensity of the first oscillation. A high ratio means the secondary shock waves are less likely to blur the seismic section.

Young tries to raise the primary-to-bubble ratio above prior art air gun sources by reducing the amplitude of the first oscillation. Young seeks this result by spacing at least three air guns in a characteristic array. The array separates the guns from each other by a critical distance. The distance,  $D$ , is at least 1.2 times greater than  $R$ , but less than or equal to twice  $R$ .  $R$  is the maximum radius of the initial air bubble from each gun. \* With this spacing, the bubbles from each gun intersect before any single bubble reaches its maximum radius. This intersection dampens the overall oscillation. Young's independent claims each include a spacing limitation within this range.

\* Mathematically,  $D$  is defined by 1.2  $R$  less than or equal to  $D$  less than or equal to 2.0  $R$ .

[\*\*4] Independent claim 1 is illustrative:

A method of producing a seismic pulse in a body of water, including the steps of:

(a) disposing in the water a set of at least three air guns, each adapted to produce in the water a gas bubble having maximum radius substantially equal to the quantity  $R$ , where the guns are disposed at depths such that each produces, when fired, a bubble of maximum radius  $R$ , and the guns are disposed such that each gun is separated from each of the nearest guns thereto in the set by a critical distance,  $D$ , where  $D$  is substantially equal to square root  $2R$ ; and

(b) firing the air guns substantially simultaneously to produce a seismic pulse in the water.

Young's dependent claims define the number of the guns or their placement relative to each other or to the ocean surface.

The examiner rejected each of the claims as obvious under 35 U.S.C. § 103 in light of five prior art references. The examiner relied primarily on U.S. Patent No. 2,619,186 to Carlisle (the "Carlisle patent" or "Carlisle")

to reject Young's claims. Carlisle is the only reference cited by the examiner or Board which suggests the air gun spacing in Young's claims.

Young contested the Board's [\*\*5] and the examiner's consideration of Carlisle. Young argued that Carlisle concerns reducing bubble oscillation for chemical explosives, not air guns. Young also argued that an article by Knudsen published six years after Carlisle in the journal *Geophysics* expressly discredits the teachings of Carlisle. W. Knudsen, *Elimination of Secondary Pressure Pulses in Offshore Exploration (A Model Study)*, 23 *Geophysics* No. 3 at 440 (July 1958) (Knudsen). Therefore, Young contended, a person of ordinary skill in the seismic exploration art would not have considered Carlisle when developing an improved seismic array.

The Board rejected Young's arguments. The Board held that the examiner appropriately applied Carlisle notwithstanding the teachings of Knudsen. On appeal, Young asserts as error only the propriety of applying Carlisle as a reference in light of Knudsen's allegedly contrary teachings.

#### DISCUSSION

This court must decide whether the Board properly affirmed the examiner's rejection over Carlisle. Young has not challenged the other references cited in the examiner's rejection. Further, Young has not argued the merits of any particular claim apart from the others. Therefore, all claims [\*\*6] stand or fall together with representative independent claim 1. See *In re Kaslow*, 707 F.2d 1366, 1376, 217 U.S.P.Q. (BNA) 1089, 1096 (Fed. Cir. 1983).

The Carlisle patent -- "Seismic Exploration Method" -- issued on November 25, 1952. Carlisle concerns minimizing bubble oscillation for chemical explosives used in marine seismic exploration. Carlisle controls bubble oscillation by spacing seismic sources to achieve a reduction of the secondary pressure pulse. Carlisle specifically [\*\*591] teaches spacing the seismic sources close enough to allow the bubbles to intersect before reaching their maximum radius. Carlisle spaces the bubble centers closer than two maximum bubble radii, or less than "2.0  $R$ " in Young's notation. Carlisle, col. 3, lines 57-60. Carlisle explains:

The secondary energy normally available from these sources is dissipated by their mutual intersection and tends to eliminate the secondary seismic impulses created when the walls of the bubbles collapse.

*Id.* at lines 60-64. Thus, Carlisle expressly teaches the spacing limitation in each of Young's claims.



Notwithstanding Carlisle's teachings, Young argues that the Knudsen article discredits Carlisle. Knudsen describes a series [\*\*7] of tests which evaluated four proposed techniques for suppressing bubble oscillation. Carlisle was one of the four. Knudsen's article opined that Carlisle yields no appreciable improvement in bubble oscillation suppression. The effective teaching of the Knudsen/Carlisle combination, Young argues, suggests avoidance of the spacing suggested in Carlisle. Therefore, Young would have this court conclude that his use of Carlisle's spacing would not have been obvious.

Young misunderstands the effect that Knudsen has on Carlisle. The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. (BNA) 871, 881 (CCPA 1981). Even if tending to discredit Carlisle, Knudsen cannot remove Carlisle from the prior art. Patents are part of the literature of the art and are relevant for all they contain. *In re Lemelson*, 55 C.C.P.A. 1294, 397 F.2d 1006, 1009, 158 U.S.P.Q. (BNA) 275, 277 (CCPA 1968). For example, in *In re Etter*, 756 F.2d 852, 859, 225 U.S.P.Q. (BNA) 1, 6 (Fed. Cir.), cert. denied, 474 U.S. 828, 88 L. Ed. 2d 72, 106 S. Ct. 88 (1985), a reference which disclosed obsolete technology remained in the prior art. This court considered the reference [\*\*8] for what it disclosed in relation to the claimed invention.

When prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill. The Board must consider all disclosures of the prior art, *In re Lamberti*, 545 F.2d 747, 750, 192 U.S.P.Q. (BNA) 278, 280 (CCPA 1976), to the extent that the references are, as here, in analogous fields of endeavor and thus would have been considered by a person of ordinary skill in the field of the invention. The Board, in weighing the suggestive power of each reference, must consider the degree to which one reference might accurately discredit another.

As prior art, the Board correctly weighed Carlisle to determine the patentability of Young's claims. Carlisle expressly teaches both the method and the advantages of Young's claimed spacing. In fact, Carlisle expressly teaches the exact spacing set out as a limitation in Young's claims. Thus, the Board correctly attributed significant weight to Carlisle in its obviousness determination.

In determining what weight to accord to Carlisle as prior art, the Board also appropriately considered Knudsen's discrediting effect. [\*\*9] The Board determined that Knudsen did not convincingly discredit Carlisle. Therefore, the Board appropriately concluded that Knud-

sen would not have led one skilled in the art to reject Carlisle.

Knudsen did not test Carlisle according to its teachings. For instance, Knudsen did not use an explosive charge in modeling Carlisle. Rather, Knudsen tried to simulate Carlisle with a capacitive electrical discharge in a barrel of oil.

Knudsen did not replicate Carlisle's teachings on spacing. Knudsen tried to model Carlisle by separating the seismic sources by one, two and three bubble radii. Knudsen at 42. At the maximum spacing of three bubble radii, the bubbles will not intersect at all. Carlisle specifically requires spacing to permit bubble intersection. Carlisle, col. 4, lines 47-52. At a spacing of one bubble radius, the two bubbles coalesced into one before the initial collapse. Knudsen at 45. If just one bubble is present, the bubble will oscillate as if [\*\*592] no second seismic source was present. Carlisle specifically requires spacing to prevent the formation of one bubble. Carlisle, col. 4, lines 34-37. Finally, at the two bubble radii spacing in Knudsen, the bubbles will just barely [\*\*10] intersect. Carlisle requires that the bubbles intersect before each bubble achieves its maximum radius. Carlisle, col. 3, lines 58-60. In sum, Knudsen did not duplicate or appropriately model Carlisle's spacing.

Knudsen's conclusion that Carlisle would "not be effective in eliminating the secondary pressure pulse" also directly contradicts data contained in Knudsen. The Knudsen data point for the two-radii horizontal bubble spacing, although not a completely accurate model of Carlisle, shows a 30% reduction of the secondary pressure pulse. Knudsen at 45, Table 4. This data point represents the only point where Knudsen approximates the spacing shown in Carlisle. At that point, Knudsen confirmed Carlisle's teachings.

The Board found that Knudsen "did not test the Carlisle technique under conditions which are directly comparable to the Carlisle disclosure." Weighing the discrepancies between the Knudsen model and Carlisle's teachings, as well as Knudsen's tendency to confirm Carlisle where the model approximated Carlisle, the Board concluded: "we do not agree that Knudsen discredits Carlisle."

Because Knudsen did not accurately test Carlisle, an artisan of ordinary skill would not have [\*\*11] dismissed Carlisle in light of Knudsen as a whole. It is far more likely that the skilled artisan would have afforded little weight to Knudsen itself. The Board did not err in relying on Carlisle and discounting Knudsen.

#### CONCLUSION

Knudsen is not so credible or persuasive of a contrary teaching that it would have deterred the skilled arti-



927 F.2d 588, \*, 1991 U.S. App. LEXIS 3386, \*\*;  
18 U.S.P.Q.2D (BNA) 1089

san from using the teachings of Carlisle. The examiner's  
use of Carlisle in his rejection of Young's claims is not

clearly erroneous. The Board's decision affirming the  
examiner's rejection is therefore

**AFFIRMED.**

**10. RELATED PROCEEDINGS APPENDIX ((37 CFR 41.37 (c)(1)(x))**

Not applicable